CSS

ICP Data Storage System

CSS 112 112

Ann Richard
NCCT
IO

Topic/Theme

1 Inherency

Project

1.1 Determining, Characterizing, and Curating Inherent Chemical Properties (ICP)

Task Description

This task is focused on significantly expanding the DSSTox chemical inventory and incorporating enhancements to facilitate processing, modeling and mining of ICP in association with toxicological and biological activity data, exposure parameters, and use-cases. These efforts will consolidate into a standard format a wide range of chemical inventories aligned with EPA regulatory and research priorities (OPP, HPV, EDSP, ECOTOX, ToxCast, Tox21, ToxRefDB, etc.), as well as provide linkages to and broad coverage of chemical-property-biological activity space that can best inform ICP calculations and models for predicting human and ecological adverse effects. This ICP chemical structure data inventory will serve as a central resource for the automated generation of a wide array of calculated properties, features, fingerprints and chemical representations, as well as for structure-based mining of chemical-activity data for modeling and hypothesis generation. In addition, this public ICP resource will promote strict adherence to quality data standards and cheminformatics interoperability, and fuel innovation in structure-activity relationship modeling and green chemistry design for environmental sustainability.

Rationale and Research Approach

ICP is recognized to have a profound influence on chemical transport, fate, persistence, exposure, and biological interactions that can lead to adverse health effects in humans and wildlife species. In addition, ICP determines the desired function and performance of substances in products and, thus, is an important consideration in green chemistry design. Identifying, characterizing, and relating key ICP metrics with a chemicals functional properties, transport, exposure, and biological effects is essential for development of predictive models, is a key component to nearly every other CSS Research Topic, and provides a basis for developing a comprehensive design strategy for sustainability. Chemical structure is not only the lingua franca of chemistry, but it encodes the basic information from which all calculated and measured ICP, and biological interactions and outcomes, are derived. Hence, the accurate indexing and representation of chemical structures linked to test substance information (both generic and sample-specific) in association with biological or exposure data is a key requirement of ICP research and ensures data quality and integrity of EPAs CSS program. A centralized database containing large, standardized inventories of chemical structures associated with tested substances and data, in turn, fuels the multiple objectives of ICP research. DSSTox is an internationally recognized public resource that provides high quality chemical structure-data files designed for use in chemical structure mining and modeling applications. As a result, DSSTox structures are being used in EPA projects (e.g., OPPTs AIM, OPP-ToxRefDB, OEI, OSP/NCEA Hydrofracking), other Agencies (e.g., FDA CFSAN, NIEHS NTP, NIH NCGC), industry (P&G, Dupont, etc.) as well as European REACH projects (e.g., OpenTox, COSMOS, etc.), and have been utilized in a wide range of Structure-Activity Relationship (SAR) modeling studies. DSSTox structure-data files are routinely searched on the Internet through the DSSTox on-line structure browser, and have also been incorporated into a wide range of on-line chemical resources, such as PubChem, ACToR and ChemSpider. In addition to downloadable, annotated structure-data files, what distinguishes the DSSTox project from these other large chemical resources is its focus on: 1) accurate expert-curated chemical structures assigned to

generic test substances; 2) quality reviewed annotation of generic test substances (CASRN, names, etc.) in association with published toxicity and bioactivity data; 3) additional chemical annotations and mapping indices (parent SMILES, salt, complex, stereochemistry, test substance description, etc.) that facilitate creation of SAR-ready structure-data files for modeling applications and encourage strict chemical data standards and model transparency. The DSSTox Master structure/substance inventory currently contains over 13K, high quality structures for chemicals of toxicological relevance and/or of high interest to EPA programs (including HPVIS, IRIS, ToxCast and ToxRefDB). This Master file is being expanded in this task to cover test substance information for over 4000 test samples plated and undergoing testing in EPAs high-throughput screening (HTS) programs (ToxCast, e1k, Tox21), as well as to provide central chemical management of test substances for the entire 10K Tox21 test substance library. In addition, this task will significantly expand the public DSSTox inventory to include thousands of external, high quality curated structures (ECOTOX, FDA PAFA) associated with toxicity data across a broad range of chemical use categories (pesticides, industrial, antimicrobial, food-additives, drugs, cosmetics ingredients, etc.). In so doing, EPA will provide an unrivaled public chemical inventory and quality resource for structure-based modeling, cheminformatics, green chemistry applications, and data mining in relation to bioactivity and toxicity outcomes. DSSTox structure inventories will be published with summary toxicity data suitable for building SAR modeling training sets (e.g., public Developmental Toxicity datasets combined from EPA, FDA and ILSI data), facilitating and providing direction for these activities. DSSTox structure indexing of Tox21 and ToxCast HTS chemicals, in turn, will encourage integration of HTS and SAR modeling approaches towards more effective data mining and predictive modeling strategies. This research aims not only to significantly expand the DSSTox Master structure/substance inventory, but also to utilize in-house and open-source capabilities to enhance this inventory with structure-use category mappings and identifiers to facilitate creation of SAR-cheminformatics-ready files while maintaining appropriate linkages to experimental data and outcomes. CSS modeling and analysis of chemical assay results, such as produced in the ToxCast and Tox21 HTS programs, require access to many levels of resolution of chemicals, including, in order of detail: 1) analytical determinations, and source-provided documentation of chemical identities, purity, solubility, concentration, etc.; 2) substance annotations accurately derived from supplier-provided information and quality review (CASRN, chemical name, degree of hydration, etc.); 3) accurate molecular structure-substance representations (mol file, SMILES, InChI, etc.) that capture appropriate levels of known stereochemistry, salt or complex form, etc.; and 4) mapping indices and explicit incorporation of parent compounds into the main inventory to facilitate parent-salt-complex-mixture-stereo family groupings for aggregating data by level of structure resolution. Mapping of the DSSTox Master inventory to known use-categories such as obtained from multiple data resources within ACToR, and Agency regulatory listings (pesticides, industrial chemicals, food-additives, fragrances, antimicrobials, drugs, etc.) can provide important cheminformatics insight into areas of chemical feature-property space linked to functional-use activity, as well as to specific adverse effect activities linked to data rich use categories (e.g., drugs vs . pesticides). ACToR has made significant strides in aggregating data for hundreds of thousands of chemicals primarily on the basis of CASRN identifiers. The DSSTox structure inventory will be used to enhance the quality of CASRN and structure associations within ACToR, as well as in other large EPA chemical resources, such as the SRS system, and public inventories, such as PubChem and ChemSpider. DSSTox structures used for the generation of a broad range of chemical descriptors, physical and reactivity properties, features and fingerprints (Projects 1.1 and 1.3) will, in turn, be commonly indexed back to the central DSSTox structure inventory and IDs, enabling broader linkages and computational applications. Finally, to encourage further adherence to the data quality standards associated with chemical structures and ICP, this task will establish a workflow to incorporate new and existing chemical substances of interest and relevance to various EPA programs. Impact: Results from this research task will lay a firm chemical foundation for all ICP-based research (Projects 1.1 and 1.3), and will enforce high standards for chemical structure annotations and data associations across the entirety of the CSS research portfolio. Products from this task will be publically available in a variety of downloadable formats and searchable applications, and fully integrated within the Dashboards and Decision Support Framework. Furthermore, the results of this research will enrich public chemical-data resources with high quality structures, annotations and linkages to EPA data and programs, will establish and promote strict standards for chemical-structure-data associations, and will spur research, collaborations, and innovation in structure-based modeling, predictive toxicology, and green

chemistry by the scientific community at large.

Outputs from Projects related to this task

(1)DSSTox SAR-ready files, including ToxCast, Tox21, ECOTOX, FDA PAFA inventories, accessible as downloadable files, and updated, enhanced DSSTox Master file incorporated into on-line EPA and external structure-browsers and EPA Dashboard. (2)On-line structure-registry queue and workflow to update DSSTox Master inventory, and link new structures to ICP calculators, properties and data within the CSS Dashboard.

Expected Products

(2) Create SAR-ready structure-property data sets for EPA ToxCast/Tox21 project inventories and generate toxicity-informed feature sets, molecular fingerprints, and property-based analog groupings for use in data-mining and modeling of ToxCast/Tox21 data, and for broader application to screening and green chemistry design.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(3) Update the DSSTox Master structure inventory with two improvements: 1) use-categories, such as pesticides, food-additives, drugs, industrial use, etc and (2) structure-category-mapping relationships (e.g., parent, salt, stereoisomer, analog, metabolite, etc.) to be used for data-mining and modeling, and green chemistry design.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(4) Extend searchability, linkages, and structure-data-mining enhancements of DSSTox ToxCast, Tox21 and ECOTOX content through incorporation in PubChem, ACToR, and the CSS Dashboard.

Type: DATA
MAP

Delivery Date (FY): 2016

(5) Create workflow to add & QC all EPA chemical structures of interest, and to integrate DSSTox structures and structure-searchability with CSS data-generating Tasks, such as in Projects 1.1, 1.3 and Dashboard.

Type: OTHER

Delivery Date (FY): 2016

(1) Deliver high quality DSSTox structure inventories in standardized, searchable format for nearly 10,000 compounds in ToxCast/Tox21, and for many thousands more in ECOTOX and FDA CFSAN compound inventories.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

Start Date Q1 2012

End Date Q4 2014

Cross Research Project Output Supported?
Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NCCT: P. Volarath, R. Judson NHEERL: C.

External Collaborators (known or proposed)

TBD

Russom NERL: D. Chang, R. Goldsmith, C. Grulke

Milestones

(Product 1) Publish final ToxCast, e1k and Tox21 chemical structure inventories as DSSTox files in downloadable form.	Scheduled: Q2 - 2012 Completed:
(Product 1) Finalize DSSTox data inventories for ToxCast and Tox21 chemical inventories and incorporate into EPA NCCT resources, ACToR and ToxMiner.	Scheduled: Q3 - 2012 Completed:
(Product 1) Incorporate full ECOTOX library of chemical structures into the DSSTox Master file and make publicly available as a downloadable file and through on-line structure browsers.	Scheduled: Q1 - 2013 Completed:
(Product 1) Incorporate full FDA PAFA library of chemical structures into the DSSTox Master file and make publicly available as a downloadable file.	Scheduled: Q2 - 2013 Completed:
(Product 2) Establish standard procedures for processing and representing DSSTox structure-data files as SAR-ready data files.	Scheduled: Q4 - 2012 Completed:
(Product 2) Create SAR-ready version of the DSSTox Master substance inventory for use in ICP research and modeling applications.	Scheduled: Q2 - 2013 Completed:
(Product 2) Publish SAR-ready DSSTox files for ToxCast, e1k and Tox21 inventories.	Scheduled: Q3 - 2013 Completed:
(Product 2) Coordinate with Tasks 1.1.1 and 1.1.3 to process SAR-ready DSSTox Master substance inventory through available property and feature calculators (EPISuite, SPARC, DEREK, Molecular Networks, etc.)	Scheduled: Q4 - 2013 Completed:
(Product 2) Provide linkages to properties, features, and molecular fingerprint resources computed on DSSTox structures for use in modeling.	Scheduled: Q1 - 2014 Completed:
(Product 3) Identify public resources to be used for annotating the DSSTox Master file with high-level use-category information.	Scheduled: Q1 - 2014 Completed:
(Product 3) Incorporate use-categories into the DSSTox Master substance inventory file for public dissemination.	Scheduled: Q3 - 2014 Completed:
(Product 3) Update the DSSTox data model to incorporate structure-category mappings to facilitate analog groupings and data mining applications.	Scheduled: Q1 - 2015 Completed:
(Product 3) Publish updated data model content for Tox21/ToxCast inventories.	Scheduled: Q3 - 2015 Completed:
(Product 3) Publish updated data model content for DSSTox Master file.	Scheduled: Q4 - 2015 Completed:
(Product 4) Incorporate updated DSSTox Master file in ACToR.	Scheduled: Q3 - 2012 Completed:

(Product 4) Incorporate updated DSSTox Master content for ToxCast/Tox21 inventories into DSSTox structure browser.	Scheduled: Q4 - 2012 Completed:
(Product 4) Incorporate updated DSSTox Master content for ECOTOX and PAFA inventories into DSSTox structure browser.	Scheduled: Q4 - 2013 Completed:
(Product 4) Publish DSSTox Tox21 and ToxCast inventories in PubChem.	Scheduled: Q2 - 2015 Completed:
(Product 4) Incorporate all DSSTox content into chemical mining capabilities within the CSS Dashboard.	Scheduled: Q2 - 2016 Completed:
(Product 5) Develop a QC check-list and scoring system to dictate level of review required prior to registration.	Scheduled: Q2 - 2014 Completed:
(Product 5) Create on-line submission form on the EPA Intranet for adding new DSSTox substances.	Scheduled: Q1 - 2015 Completed:
(Product 5) Create on-line submission form on the Internet for registering adding new DSSTox substances.	Scheduled: Q2 - 2016 Completed:
(Product 5) Implement workflow to populate updated DSSTox Master substance inventory with ICP properties and features implemented within the CSS Dashboard.	Scheduled: Q4 - 2016 Completed:

Division Approved Yes

CSS

ICP Generation for QSAR & Model-Building

CSS 113 113

Ann Richard
NCCT
IO

Topic/Theme

1 Inherency

Project

1.1 Determining, Characterizing, and Curating Inherent Chemical Properties (ICP)

Task Description

This task is focused on the challenges of predicting key chemical transformations in environmental media and biological systems that impact fate, transport, and in vivo toxicity. Research will include refinement and testing of the SPARC (SPARC Performs Automated Reasoning in Chemistry) process models, and extensions of these models to additional physico-chemical properties that describe the reactivity, speciation, transport and fate of organic pollutants in the environment. SPARC enhancements will be incorporated into a Physico-Chemical Properties Module that will provide direct linkage to EPI Suite and SPARC tools for calculation of ICP necessary for parameterization of environmental fate and transport models. Additional research within this task will focus on using expert toxicity and metabolism prediction systems (DEREK and METEOR), based on use of structural features, to create a computational workflow to predict areas of chemical space where in vivo toxicity (e.g., rat carcinogenicity) is more likely to be impacted by metabolism (i.e., where metabolism is required to produce toxicity). This workflow will be applied to the large ToxCast and Tox21 inventories currently undergoing testing in HTS assays, many of which lack metabolic capability, in order to guide and improve in vitro to in vivo modeling outcomes.

Rationale and Research Approach

ICP derived from chemical structure is an essential determinant of chemical transport, fate, persistence, exposure, and biological interactions that can lead to adverse health effects in humans and wildlife species. A chemical can be uniquely identified, indexed and linked to ICP and experimental data through its molecular structure. However, a molecular structure, and its inherent chemistry, is not immutable. In environmental media or biological systems, chemicals may undergo chemical speciation or transformations that can profoundly impact environmental fate and transport, bioavailability, and adverse outcomes in humans and ecological species. In the environment, such transformations are primarily driven by intrinsic chemical reactivity mediated by environmental factors, and include environmental transformation processes such as abiotic oxidation, reduction, hydrolysis, photolysis, as well as aerobic and anaerobic biodegadation. Within biological systems, metabolism is the major engine of biotransformation. Failure to account for chemical transformations in calculating ICP inputs to fate and transport models can lead to grossly inaccurate and inadequate model outcomes. By the same token, lack of metabolism in high-throughput screening (HTS) assays can lead to discordant in vitro and in vivo results, impacting computational models that rely primarily upon HTS results to predict in vivo outcomes. This task will focus specifically on these two major problem areas of ICP research, with development of methods to predict properties and features that can anticipate environmental and biological transformations as they pertain to modeling of fate and transport, as well as in vivo animal toxicity. A key Agency need identified as a high priority in the CSS research program is for high throughput computational systems to simulate environmental fate and transport for a myriad of chemicals for which environmental data are not available. A prerequisite for such a capability is an understanding of the ICP required for the prediction of reaction rates, pathways, transformation products and partitioning behavior. Physico-chemical properties such as these have been experimentally measured for less than 1 percent of the approximately 84,000 chemicals on the TSCA inventory and 100,000 chemicals registered in the European REACH Program; further, each year

approximately 1,000 new industrial chemicals and pesticides are introduced into commerce. Physical properties frequently used in environmental assessment include vapor pressure, boiling point, solubility, partition coefficient, Henrys constant, and diffusion properties. Chemical reactivity parameters such as ionization constants, partition coeffecients and rate constants for transformation processes are also critical determinants of a chemicals environmental fate. Even when measured values are available, reported experimental discrepancies are common and values may be of questionable validity. Both in the environment and within the bodies of living organisms, many types of chemicals are known to equilibrate to multiple chemical forms (i.e., speciation) that can differ dramatically in their chemical and physical properties. These can include complex chemical species such as ions, zwitterions, tautomers or hydrates. In addition, the speciation of a given chemical is highly dependent on environmental system conditions (temperature, pH, ionic strength) and medium composition (gas, liquid, solid components). SPARC uses computational algorithms based on fundamental chemical structure theory to estimate a large array of physiochemical property parameters strictly from molecular structure. SPARC predicts numerous chemical reactivity parameters and physical properties that provide essential inputs to fate and transport models as a function of environmental conditions such as media, temperature, pressure and pH, and is sufficiently parameterized to cover a broad range of organic chemical space. This research task will include refinement and testing of the core SPARC process models, and extensions of these models to additional physical and chemical properties that describe the reactivity, transport and fate of organic pollutants in the environment. SPARC is also being incorporated into a Physico-Chemical Properties Calculator (PPC), currently under development, that will provide the user with molecular descriptors obtained from mechanistic, QSAR-based and quantum mechanical-based calculators. Modeling software technologies such as D4EM (Data for Environmental Modeling) developed through ORDs Integrated Environmental Modeling (IEM) Program will provide the user direct linkage to molecular calculators such as EPI Suite and SPARC, as well as seamless access to databases of measured physico-chemical properties. These data will be stored in a database that is searchable by structure and substructure, stores the accompanying meta data, and provides an uncertainty analysis of the data collected from the various calculators and databases. Project outputs and capabilities will be integrated with other areas of ICP research, to cross-reference database structures to the DSSTox inventory, to include calculators within ICP and QSAR modeling workflows, to use domain of applicability approaches to evaluate models, and to be accessed through the CSS Dashboard. A second area of research in this task is focusing on using existing knowledge-bases and cheminformatics approaches to predict areas of chemical space where metabolism has a greater likelihood of influencing in vivo animal toxicity outcomes. Models are being built to predict in vivo toxicity from bioactivity profiles, e.g., ToxCast and Tox21 high-throughput screening (HTS) assay results. However, since many of these HTS assays currently lack metabolic capabilities, they may produce results that do not relate to in vivo toxicity for those compounds requiring metabolic activation for toxicity to be expressed. DEREK is astructure-activity relationship (SAR) prediction system, widely used in government and industry, that relies primarily upon expert judgement and existing data to associate chemical features (structural alerts) with particular in vivo or in vitro toxicity outcomes (e.g., rat or mouse carcinogenicity, developmental toxicity, genetic toxicity, etc.). METEOR is an expert rule-based SARsystem that predicts possible metabolic transformations from molecular structure based on recognition of parent structural features (e.g., an aromatic nitro group in mammalian systems would be assumed to undergo reduction to an aromatic amine, which is associated with a number of toxicities). DEREK works by recognizing toxicity alerting features, but has limited knowledge of when such features require metabolic transformation to produce toxicity. METEOR is built on an entirely different knowledge base pertaining to metabolic transformation rules (i.e., feature A is metabolized to feature B) and has no explicit knowledge of toxicity. Hence, a library of parent compounds can be processed through METEOR to produce a range of possible daughter metabolites, and both the parent and daughter compounds can be processed through DEREK to provide a more realistic estimate of potential toxicity of the parent (and metabolites) in in vivo systems. An automated computational workflow will be developed to process large DSSTox SAR-ready structure files associated with the ToxCast and Tox21 HTS research programs through METEOR, with the results processed through DEREK to identify areas of chemical space within these inventories where metabolic transformation changes the DEREK parent chemical prediction, i.e., implying either metabolic activation or deactivation. Structural features that are linked by the METEOR transformation rules to DEREK

structural alerting features for a particular toxicity endpoint will be extracted from this process and used to predict areas of chemical space where metabolic activation or deactivation is more probable. Such knowledge can be used to inform and guide the construction of hybrid structure-HTS in vitro models of in vivo toxicity when HTS assays are lacking in metabolic capability and, thus, improve the focus and overall accuracy of such models. DEREK predictions (i.e., detecting a structure-alerting feature) across all modeled toxicity endpoints can also be used to generate a toxicity alert profile, or fingerprint, of each chemical within an inventory, such as Tox21. Such toxicity-informed chemical fingerprints represent a more highly processed ICP relating to toxicity that can be used like any other set of ICP and chemical descriptors for modeling and data mining, and for creating chemical analog groupings and neighborhoods for more focused data inquiry. Features and fingerprints derived from the METEOR and DEREK analyses of ToxCast and Tox21 chemicals will be included as part of the larger ICP data inventory to be incorporated into other CSS tools and the CSS Dashboard. Both of the above research efforts will be coordinated with other ICP research (Task 1.1.1 and 1.1.3) to process DSSTox structures for use in computing various types of ICP (e.g., phys-chem properties, reactivity parameters, toxicity-informed features), as well as in the generation of molecular features and fingerprints, such as extracted from DEREK. Open source software will be used to create an automated workflow for processing structures to generate ICP, or to incorporate results from external programs (SPARC, EPI Suite, through the Physico-Chemical Property Calculator, and METEOR and DEREK). Processed structures, features, and associated properties will be incorporated into aggregated data resources (ACToR), analysis tools (ToxMiner) and CSS Dashboard technologies for enabling data-mining and for building meaningful chemical categories and nearest neighbor analog groups. These will developed in collaboration with SAR experts within OPPT and will be used to augment and expand existing analog identification methodologies, such as incorporated in the OPPT AIM software and OECD Toolbox. Impact: Results of this task will provide EPA Program Offices and other regulators with ready access to ICP pertaining to predicting key chemical transformations in environmental media and biological systems for enhancing risk assessment activities and prioritizing toxicity-testing requirements for regulated chemicals. SPARC and EPI Suite will provide physical properties, chemical reactivity models and parameters characterizing the complex processes influencing reactivity, environmental fate and transport of chemicals as a function of environmental conditions. These outputs will be used to develop and apply various Agency models (e.g., Environmental Fate Simulator, Reaction Pathway Simulator, Physico-Chemical Property Calculator). Results from the METEOR+DEREK workflow applied to the ToxCast and Tox21 chemical libraries will be used to compensate for current limitations in HTS assay technologies (i.e., many lack metabolism) to guide and improve models and toxicity signatures relating HTS in vitro profiles to in vivo outcomes.

Outputs from Projects related to this task

(1) Physico-Chemical Properties Calculator, linked to EPI Suite and enhanced SPARC capabilities, provides molecular descriptors for the parametrization of environmental fate & transport models. (2) Integration of Physico-Chemical Properties Calculator with outputs of Tasks 1.1.1 and 1.1.2 to supply ICP for chemicals of Agency interest and to provide key descriptors for environmental fate & transport models accessed through the CSS Dashboard. (3)Ability to predict areas of chemical space more likely to require metabolic activation to produce an in vivo outcome, incorporated within an automated cheminformatics workflow (coordinated with Tasks 1.1.1 and 1.3.2) and linked to other precomputed ICP and toxicity informed DEREK feature profiles for use within CSS Dashboard.

Expected Products

(2) Development of a Physico-Chemical Properties Module that will provide direct linkage to EPI Suite and SPARC tools for the calculation of the molecular descriptors necessary for the parameterization of environmental fate and transport models

Type: DATA
MODEL

Delivery Date (FY): 2013

(3) Extend and Refine the SPARC models for the calculation of hydrolysis rates constants for

chemical classes of interest

Type: DATA MODEL — Delivery Date (FY): 2014

(4) Extend and refine the SPARC models for the calculation of molecular descriptors required for the parameterization of QSARs (i.e., electron affinity and E1 reduction.

Type: DATA MODEL — Delivery Date (FY): 2015

(5) Develop workflow to use SAR knowledge-bases (DEREK, METEOR) to predict chemical space where in vivo toxicity is likely mediated by metabolism, guiding interpretation and modeling of HTS in vitro responses.

Type: DATA MODEL — Delivery Date (FY): 2013

(1) Improve the SPARC speciation models for chemical ionization, tautomerization and hydration to improve fate and transport models and enhance chemical risk assessment.

Type: OTHER — Delivery Date (FY): 2012

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

TBD

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Refine and test speciation models using experimental pKa data in aqueous solution gathered from the literature	Scheduled: Q3 - 2012 Completed:
(Product 1) Additional refinement and testing of speciation models via prediction of aqueous pKa based on literature available non-aqueous pKa data	Scheduled: Q4 - 2012 Completed:
(Product 2) Develop a list of the environmental fate and transport models currently in use by OPPT and OPP for predicting environmental concentrations	Scheduled: Q1 - 2013 Completed:
(Product 2) Based on the list of EF&T models determine the physico-chemical properties required for parameterization of the models	Scheduled: Q3 - 2013 Completed:
(Product 2) Develop linkages between EPI Suite and SPARC calculator with a structure-searchable data base	Scheduled: Q4 - 2013 Completed:
(Product 2) Coordinate linkages of Module with DSSTox structure database and CSS Dashboard	Scheduled: Q4 - 2013

(Product 3) Collect literature derived experimental data for hydrolysis of epoxides and halogenated alkanes	Completed: Scheduled: Q2 - 2014
(Product 3) Develop mechanistic model for hydrolysis based on experimental data for the epoxides	Completed: Scheduled: Q4 - 2014
(Product 4) Use QSAR and quantum mechanical calculators to generate data set of reduction potentials for reducible compounds to train SPARC models	Completed: Scheduled: Q3 - 2014
(Product 4) Use QSAR and quantum mechanical calculators to generate data set of bond strengths for halogenated alkanes to train SPARC models	Completed: Scheduled: Q4 - 2015
(Product 5) Compile scripts to create automated workflow for processing of SAR-ready files through METEOR and DEREK.	Completed: Scheduled: Q2 - 2012
(Product 5) Validate and refine workflow by comparing predictions to metabolically resolved NTP genetox data for over 1500 compounds.	Completed: Scheduled: Q4 - 2012
(Product 5) 5.3 Apply workflow to predict chemical space within ToxCast and Tox21 inventories where metabolism is likely to impact rat carcinogenicity in vivo response.	Completed: Scheduled: Q1 - 2013
(Product 5) Extend predictions to other in vivo endpoints predicted by DEREK.	Completed: Scheduled: Q2 - 2013 Completed:

Division Approved Yes

CSS Identify Key ICP and Define Chemical Space of Interest to EPA

CSS 111 111

Danny Chang
NERL
HEASD

Topic/Theme

1 Inherency

Project

1.1 Determining, Characterizing, and Curating Inherent Chemical Properties (ICP)

Associated Project

None

Task Description

Identifying key ICPs and defining chemical space of interest to EPA will provide the impetus for the initiation of focused research efforts to decrease the uncertainty of methods and models the Agency uses to protect human health and environment. The research performed within this task will also support ongoing research. A key component to this task is the identification and enumeration of key ICP that capture salient features of chemicals or chemical classes that are important for characterizing and modeling function, hazard, fate, and exposure. Identification of these key properties also supports and promotes sustainable practices through ICP-based principles of green chemistry, which will avoid, or at least limit, future environmental problems.

Rationale and Research Approach

Currently, there are more than 100,000 chemicals registered in the European Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) Program; 84,000 chemicals on the Toxic Substances Control Act (TSCA) inventory; and each year about 1,000 new industrial chemicals and pesticides are introduced into commerce. In many cases for industrial chemicals, assessment of risk is challenging due to limitations in existing data, tools and resources. In the context of existing data limitations, current human health and ecological risk assessment approaches require a paradigm shift to one that better utilizes the relationships between a chemicals ICP and its exposure and hazard potential. The approach to this research will consist of reviewing a subset of the existing compilation of OCSPP/OW/ORD models the Agency uses in risk assessment and risk management, and then applying computational and statistical approaches to rank the importance and reliability of specific ICP used in these models to a select number of chemicals and/or chemical classes. Specific ICP include, but are not limited to: 2-D and 3-D chemical structure representations (molecular topology) including stereochemistry; 2-D and 3-D molecular descriptors; fate, transport, and exposure model parameters; reaction parameters and products; properties related to toxicity pathways; reference spectra for different analytical chemistry techniques; and physical aspects of engineered nanomaterials. Using the identified ICP, the chemical spaces of interest to the Agency will be defined. Each of these spaces will then be evaluated to determine where existing data are sufficient to generate reliable predictions for related chemicals (i.e., the domains of applicability) within a given model structure (i.e., ICP estimation tools). Guidance for assessing the utility of ICP-based models and methods in terms of their chemical space and domain of applicability will be developed and tested within this task. The Agencys new and current ICP estimation tools will be evaluated for their efficacy in these regions of chemical space. Identification of relevant chemical space for the Agencys interest will aid scientists and stakeholders in characterizing and defining critical data gaps among existing and new classes of chemicals and help foster integrated transdisciplinary research efforts in the development of new models and/or experiments to estimate relevant ICP (i.e., Inherency 1.3: Linking ICP to Metrics Relevant to Risk Characterization and Risk Management). Rapid computational approaches for generating molecular features from structure will be used to compute and store chemical information as molecular fingerprints for use in navigating and organizing large chemical spaces into smaller, more manageable

and chemically-meaningful categories. Key areas of focus for the research within this task will include: 1. Classification of existing and new ICP-relevant technologies (computational and experimental) within the Agency. This area will give researchers and stakeholders the statistical tools necessary to compare, evaluate, and determine the efficacy of current and emerging technologies in terms of their ICP and chemical space coordinates as well as their abilities to address chemicals of concern to the Agency (i.e., domains of applicability) in relation to existing models and methods. [Supports Products 1, 2, 3 and 4] 2. Determination, classification and development of key molecular fingerprints (signatures) to describe relevant regions of chemical space. This area will aid in harmonizing the description of chemicals through molecular fingerprints, their outcomes and their interaction to biology and the environment, as well as provide potential guidance on prioritization and screening methods, gap analysis and the development of new methods for determining derived and ICP. [Supports Products 1, 2, 3 and 4] 3. Identification and characterization for regions of chemical space relevant to Agencys current and emerging needs. This area allow the Agency to utilize molecular fingerprints and ICP to characterize regions of chemical space relevant to different aspects of the Agencys mission (i.e., exposure, hazard, adverse outcomes, risk assessment and management) in an effort to focus research efforts and determine data gaps, overlaps and redundancies. [Supports Products 1, 2, 3 and 4] 4. Utilization of chemical space to inform model development and experimental design. This area will link ICP-based chemical space knowledge to CSS Inherency Project 3 and other CSS topic areas to inform researchers and stakeholders in developing computational models and/or experimental methods/measurements in support of Agencys mission. ICP will be used to predict specific exposure, hazard, and risk-based endpoints. Research will include understanding why specific ICP, or aggregate ICP, are good or poor predictors, and will help focus ICP research efforts in other parts of the Inherency Topic. [Supports Products 1, 2 and 4] Impact: Results from this research task will be the foundation for many of the other research efforts within this project and will also aid researchers working in other CSS Topics. This research will provide an integrated data stream into other areas of Inherency and key CSS topic areas in Biomarkers, Systems Models, Life Cycle Considerations, Cumulative Risk and Dashboards. Furthermore, identification of key ICPs and well-defined chemical spaces of interest to the agency will allow for a more efficient and responsive line of research to the needs of the clients and the scientific community at large.

Outputs from Projects related to this task

(1) A resource of inherent chemical properties (ICP), molecular descriptors and selected biological activities for chemicals of interest to OCSPP. (2) Provide tools and methods for chemical space analysis and domain of applicability for models to be incorporated into Dashboards

Expected Products

(3) Interactive linked database of physicochemical parameter values for QSAR training set and test chemicals consolidated with associated biological activity parameter values (using DSSTox registered structures and feature sets, and integrating data within ACToR).

Type: DATA
DATABASE

Delivery Date (FY): 2015

(4) Case studies for application of chemical domain restricted analysis in assessing exposure and risk: pesticides and industrial chemicals.

Type: PUBLISHED REPORT
REPORT

Delivery Date (FY): 2016

(1) Framework for evaluation of domains of applicability (DoA) for use in molecular-based models.

Type: PUBLISHED REPORT
REPORT

Delivery Date (FY): 2013

(2) Case Studies for Domain of Applicability (DoA) determination and analysis using Framework. Chemicals selected in consultation with OSCPP.

Type: OTHER

Delivery Date (FY): 2014

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NERL: Goldsmith/Grulke/Chang (chemoinformatics), Dary (exposure-dose) NCCT: Judson/Richard/Volarath (database development and integration, chemoinformatics) OCSPP: TBD

External Collaborators (known or proposed)

TBD

Milestones

None

Division Approved Yes

CSS Detecting, Quantifying and Characterizing Nanomaterials

CSS 121 121

Thabet Tolaymat
NRMRL
LRPCD

Topic/Theme

1 Inherency

Project

1.2 Nanomaterial-Specific Inherency Issues

Associated Project

None

Task Description

The increasing use of nanomaterials in various products makes their release into the environment inevitable. Methodologies for the detection, quantification and characterization of these nanomaterials are thus essential in order to investigate their environmental impacts. Currently, there are some techniques for the detection and characterization of purenanomaterialssuspensions. However, the characterization and detection of nanomaterials becomes complicated in environmental samples that may contain impurities, colloids and organic materials that may interfere with the detection of these nanoparticles. Having the ability to detect, quantify and characterize these nanomaterials in various environmental systems is of a great importance to the EPA as it facilitates the risk assessment and leads to more comprehensive evaluation of the use of nanomaterials in new products.

Rationale and Research Approach

Research gap with regards to analytical capabilities for the detection quantification and characterization of nanoparticles has resulted in the identification of this research as a priority for ORD. New and existing analytical methods will be developed and refined to measure and evaluate quantities and characteristics of these nanoparticles in environmental media. These methods would also allow, in the case of metallic nanoparticles, for distinguishing metal ions from the metallic forms. Additionally these methods would assist in the identification of the specific nanomaterials inherent properties that affect their release, transport, and fate in the environment, as well as their potential exposure and adverse effects on human health which will lead to a more comprehensive risk evaluation. Under this research effort, a set of effective methodologies for detection, quantification and characterization of nanomaterials in environmental media and biological tissues will be developed using an array of laboratory-based and field screening techniques. Laboratory methods will employ advanced separation methods such as field flow fractionation (FFF) and hydrodynamic chromatography (HDC), as well as pioneering detection approaches such as single particle-inductively coupled plasma mass spectrometry (SP-ICPMS) and liquid cell atomic force microscopy (AFM) for characterizing nanomaterials in environmental samples. Analytical methods for quantifying chemical composition and speciation will include new synchrotron based high resolution micro/nano-X-ray fluorescence and adsorption spectroscopy capable of quantifying elemental chemical state and binding environments at the nanoscale and micro X-ray photoelectron spectroscopy. Leading edge sample preparation techniques for electron microscopy (EM) will allow for the first time sensitive and representative nanomaterials detection, quantification, and characterization. Remote detection and characterization of nanomaterials in the subsurface will be investigated using advanced geophysical techniques. There is a relatively large number of nanoparticles that are currently being used and their applications are expected to grow exponentially. Of these nanoparticles, four have been identified as the short-term focus of this research effort. These nanoparticles are copper (CuNPs), silver (AgNPs), cerium oxide (Ce2O) and carbon nanotubes (CNTs). Copper and silver nanoparticles are of importance because of their strong antibacterial properties which resulted in their increasing incorporation in many consumer products such as textiles, plastics and lumber. Cerium oxide is heavily used as a fuel additive with little information about its environmental fate. Finally, carbon

nanotubes (CNTs) exhibited some toxicological impacts that have to be evaluated in various environmental settings. It is expected that the long-term nanoparticles specific focus of this research effort will change to address EPAs research needs as a result of new advancements in and changes to nanomaterials applications. As a result, the focus may shift away from these nanoparticles (as more data about them is gathered) to include others that are of interest to the Agency.

Outputs from Projects related to this task

(1)Methods for the detection and characterization for the analysis of metal and carbon based nanoparticles in environmental matrices. (2) Data on the impacts of inherent particle properties and environmental conditions on their fate in environmental systems. (3) Data on the quantities and speciation of nanoparticles leaching from products containing nanomaterials.

Expected Products

(3) Develop methods for the characterizing the physical and chemical properties that influence bioavailability of nano silver.

Type: OTHER Delivery Date (FY): 2012

(7) Report characterizing Cu NP leached from treated wood

Type: PUBLISHED REPORT
REPORT Delivery Date (FY): 2013

(13) Evaluate nanoparticle geoelectrical concentration breakthrough in saturated media for development of innovative non-intrusive methodologies for detection of nanopatricles in the subsurface from anthropogenic sources

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2014

(4) Develop methods for the separation of Ag, Cu and CNT nanoparticles from environmental matrices and sample integrity maintenance at environmentally relevant concentrations.

Type: OTHER Delivery Date (FY): 2013

(5) Characterize and Assess Ag nanomaterial surface property effects on fate in Containment Systems.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2013

(6) Evaluation of characterization of the size and mixing state of ambient cerium containing particles from fuel additives based on observations and modeling

Type: OTHER Delivery Date (FY): 2013

(8) Development of sampling methods for sensitive and representative SEM/EDS analysis of environmental samples for nanomaterials in response to clients needs for methodology for sampling for nanomaterials in environmental media

Type: OTHER Delivery Date (FY): 2014

(9) Development of methods that uses advanced analytic techniques (XPS, HR-TEM, FESEM) and quantum chemistry calculations to characterize the size, surface charge and agglomeration state of CNT in the presence of environmental stressors for toxicological studies;

Type: OTHER Delivery Date (FY): 2014

(10) The development and evaluation of prototype nanosensor in response to clients needs for development of innovative methodolgies for detection of nanoparticles in environmental media

Type: OTHER Delivery Date (FY): 2015

(11) Development of laboratory and field tests, advanced analytic techniques (XPS, HR-TEM, FESEM, etc) and quantum chemistry calculations to evaluate the applications, implications and potential risks of surface-altered TiO2, CNT, Cu, ZnO and Ag nanoparticles from consumer products in environmental vectors (landfills, soil, chlorinated and brackish water, biosolids, and wetland;

Type: OTHER Delivery Date (FY): 2014

(12) Development of methods that detect, quantify, and characteriz metal-containing nanoparticles in environmental samples with two-dimensional separation techniques in response to clients needs for development of analytical methodology

Type: OTHER Delivery Date (FY): 2014

(1) Evaluation of LC/MS and electrochemical methods for the analysis of carbon nanotubes and nano-metals in environmental waters and soils.

Type: OTHER Delivery Date (FY): 2012

(2) Develop and adapt hyphenated techniques for characterizing nanoparticles (Cu, Ag or CNT) with detection by single particle-inductively coupled plasma mass spectrometry.

Type: OTHER Delivery Date (FY): 2012

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)

NRMRL: Souhail Al-Abed, Kirk Scheckel, Todd Luxton, Anthony Zimmer NERL: HEASD: Kim Rogers, Karen Bradham, Robert Willis; AMAD: Kathleen Fahey, Havala Pye; ESD: Ed Heithmar, Georges-Marie Momplaisir, Charlita Rosal, Wayne Sovocool, Katrina Varner, Dale Werkema, Tammy Jones-Lepp

External Collaborators (known or proposed)

TBD

Milestones

(Product 3) SOP on in-vitro methods for the determination of the estimated bioavailability of AgNPs.	Scheduled: Q2 - 2012 Completed:
(Product 4) First draft LC/MS and electrochemical methods for the analysis of carbon nanotubes and nano-metals in environmental waters and soils.	Scheduled: Q2 - 2012 Completed:
(Product 4) Initial Development of hyphenated techniques for characterizing nanoparticles with detection by single particle-inductively coupled plasma mass	Scheduled: Q3 - 2012

spectrometry.	Completed:
(Product 4) Draft evaluation of rotating disk technology for nanomaterial sampling.	Scheduled: Q4 - 2012
	Completed:
(Product 4) Draft methodology outlining hyphenated techniques for characterizing nanoparticles with detection by single particle-inductively coupled plasma mass spectrometry.	Scheduled: Q2 - 2013
	Completed:
(Product 5) Draft report and data on the impact of AgNPs in waste composting systems	Scheduled: Q4 - 2012
	Completed:
(Product 6) Completion of ambient field sampling of cerium oxide in Newcastle, UK.	Scheduled: Q3 - 2012
	Completed:
(Product 7) Micronized copper treated lumber sample collection and methodology finalization.	Scheduled: Q2 - 2012
	Completed:
(Product 7) Develop and evaluate methods for measuring copper ions and nanoparticles in leachates from treated wood products.	Scheduled: Q3 - 2012
	Completed:
(Product 7) Draft report and data on the mobility of micronized copper from treated lumber.	Scheduled: Q3 - 2013
	Completed:

Division Approved Yes

CSS Environmental Transport and Transformation of Nanomaterials

CSS 122 122

Richard Zepp
NERL
ERD

Topic/Theme

1 Inherency

Project

1.2 Nanomaterial-Specific Inherency Issues

Associated Project

None

Task Description

This task provides data and tools for evaluating relationships between inherent chemical properties of manufactured nanomaterials and their transport, transformation and bioavailability in environmental and treatment systems. Nanoscale metals (silver, copper/copper(II) oxide, and cerium oxide) and carbon nanotubes are included in this research. Outcomes of the research will be improved estimates of factors that affect the bioavailability of the nanometals, the persistence of carbon nanomaterials, the release of these materials from consumer products and polymer composites, and atmospheric transport of nanoscale fuel additives. The research also will lead to better predictions of the concentrations and forms of manufactured nanomaterials to which humans and ecosystems are exposed.

Rationale and Research Approach

Manufactured nanomaterials are now in more than 1,300 commercial products and have found widespread applications in diverse products such as microelectronics, disinfectants in detergents, wood preservatives, nano pesticides, fillers for plastics and rubber, cosmetics/health, medical delivery devices, and construction materials, sensors, solar energy devices, image contrast agents, and various consumer products. These materials have a number of beneficial commercial uses that have resulted in increased productivity and job creation and remediation of contaminated environments. Nonetheless, the burgeoning use of nanomaterials has prompted concerns by the U.S. government about their potential (but largely unknown) impacts on human health and the environment. The U.S. EPA has been designated as one of the lead U.S. agencies in the National Nanotechnology Initiative that is evaluating these potential impacts. There are several routes that nanomaterials can be released into the environment including (1) release from household or commercial products during intended uses, (2) release from degradation of materials such as coatings of nano-metals/metal oxides or polymer nanocomposites, (3) release from combustion of fuels with nano-ceria additives; (4) discharge from wastewater treatment plants; (5) accidental spills of materials or waste streams discharged during manufacturing. As use of nanomaterials continues to escalate, the U.S. EPA will increasingly be required to assess the environmental impact of these materials. Nanomaterials pose special challenges for inherency research because tools for relating the inherent chemical properties of these materials to their transport and transformation are different from or more difficult to define, than those used for traditional chemicals. Key exposure, effects, and life cycle assessments can vary significantly along the size/surface charge/composition/dimensionality continuum of nanoparticles, which is in turn determined by complex interactions with the environment as well as in vivo systems. Developing and refining these tools are essential in meeting key program needs in risk assessment and management for a variety of carbon-based, metal oxide, and metal nanomaterials that have already been developed for use in a wide range of commercial products. Several examples illustrate the important role played by transport and transformation in evaluating exposure and risks associated with nanomaterials. In the case of nanoscale metals, the speciation of the metal is an important determinant of its biological activity. For example, in the case of Nano-Silver particles (AgNPs), Ag+ release has been shown to be the major species that causes the observed toxicity of Ag NPs. Thus, transformation of the commercial

nanomaterial to its ionic form plays a key role in its exposure to human and non-human organisms. Moreover, atmospheric transport of the nanoscale cerium oxide (nanoceria) fuel additives likely plays a significant role in human exposure to this nanomaterial. Another example involves the release of nanomaterials from polymer nanocomposites which is caused primarily by photochemical transformation of the polymers. Moreover, interactions of nanomaterials such as carbon nanotubes (CNTs) with natural organic matter strongly influence both their aggregation and deposition, thus strongly affecting their transport, transformation, and exposure in aquatic environments. Of large number of nanoparticles that are currently being used, four have been identified as the short-term focus of this research effort. These nanoparticles are copper (CuNPs), AgNPs, nanoceria and CNTs. Copper and silver nanoparticles are of importance because of their strong antibacterial properties which resulted in their increasing incorporation in many consumer products such as textiles and lumber. Nanoceria is widely used as a fuel additive with little information about its environmental fate. Finally, carbon nanotubes (CNTs) exhibited some toxicological impacts that have to be evaluated in various environmental settings. It is expected that the focus of this research effort will change over the long term to address EPAs research needs as a result of new advancements in and changes to nanomaterials applications. As a result, the focus may shift away from these nanoparticles (as more data about them is gathered) to include others that are of interest to the Agency. Examples of the research approach include: (1) developing bioavailability tools for assessing human exposures to AgNPs. This project will provide new insights into factors that influence the biological availability of these nanoparticles including the role played by manufactured coatings on the particles. A mouse model will be developed and evaluated as part of this work. Although the project primarily focuses on human bioavailability, results also should provide useful data for ecological assessments; (2) developing a high-throughput protocol for evaluating nanomaterial transport in soils and sediments. This research and development effort would build on techniques using deep well plates packed with porous media coupled with analytical plate reader methods for the rapid determination of the transport potential of microbial pathogens through sands and sediments. (3) developing and evaluating tools that describe the deposition of CNTs including effects of changing ionic and natural organic matter composition and transformations on aggregation and deposition (measured for example by attachment coefficients and critical coagulation coefficients). One goal of the projects will be to obtain data and develop relationships that that can be used in part to link ICPs of CNTs to models that predict their transport, transformation and exposure in the environment; (4) assessing emissions to the atmosphere of nano-ceria (cerium oxide) from combustion of ceria-doped fuels. This work involves characterization of the size and mixing state of ambient cerium containing particles from fuel additives based on observations and modeling. A field project in Newcastle, UK will be completed as part of the research. (5) development of data and methods for characterizing the potential leaching and availability of CuNPs from wood products to support OPP/AD regulatory decisions. This research will seek to expand the general understanding of the potential release of CuNPs from treated wood into the environment; (6) development of data and methods for characterizing metal (Ag and Cu) nanoparticles in wastewater treatment plant effluents; (7) development of methods, analyses, and reporting on the detection, evaluation and assessment of release of nanomaterials (including carbon nanotubes) from polymer composites and consumer products. The project will focus on transformations that release CNTs from their composites with polymers and also on the correlation between the mechanical and/or chemical transformation of nanomaterials from consumer products in the presence of environmental stressors and the resulting changes in inherent properties. Identification of the specific products will be in coordination with OCSPP, ILSI, and industry which will be coordinated through a CRADA to be developed.

Outputs from Projects related to this task

(1) Tools for the bioavailability assessment of nanoparticles. (2) High throughput protocols for estimating the transport of nanoparticles in environmental systems (e.g., waste water treatment plants). (3) Experimental and modeling tools for evaluating transport and transformations of nanoparticles in the environment. (4)Data and relationships that can be used to link ICPs of nanoparticles to models that predict NP transport, transformation and exposure in the environment. (5) Data on emissions produced from the use of ceria doped diesel fuel.

Expected Products

(5) Development of data and methods for characterizing the potential leaching and availability of nano Cu/CuO from wood products.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(2) Develop high throughput protocol for estimating (Ag, Cu and CNT) nanomaterial transport in soils & sediments.

Type: OTHER

Delivery Date (FY): 2013

(3) Evaluate and detect the deposition of carbon nanotubes on environmental surfaces.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(4) Assessing emissions produced from ceria doped diesel fuel

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(6) Development of data and methods for characterizing metal (Ag and Cu) nanoparticles in wastewater treatment plant effluents

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(7) Development of methods, analyses, and reporting on the detection, evaluation and assessment of release of nanomaterials (including cnts)from polymers representative of consumer products. Identification of the specific products will be in coordination with OCSPP, ILSI, industry and operate in part through a CRADA to be developed.

Type: OTHER

Delivery Date (FY): 2013

(8) Development of detection methods and data on characterize potential translocation and transformation of CNT, Ag and Cu ENPs from source to dust and other indoor surfaces

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(9) Evaluation of the bioavailability of Cu nanoparticles through oral and inhalation exposure routes

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(10) Development of regional scale analysis of nanoparticle transport using existing transport theory

Type: OTHER

Delivery Date (FY): 2014

(11) Development of process models for the production of ROS by nanomaterials

Type: DATA
MODEL

Delivery Date (FY): 2014

(12) Evaluation of emissions source terms for use in indoor air quality models that can be used to predict concentrations in realistic environments

Type: DATA

Delivery Date (FY): 2015

SCIENTIFIC DATA

(13) Evaluation of Bioavailability of Micronized Copper from treated lumber

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(14) Linkage of inherent chemical properties to nanomaterial transformation models

Type: DATA
MODEL

Delivery Date (FY): 2016

(15) Evaluation of the influence of natural organic matter and biofilms on the transport and removal of carbon nanotubes in aqueous systems

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2016

(16) Regional scale analysis of nanoparticle transport using extended approaches that account for laboratory data developed by EPA

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2016

(17) Characterization of ambient particle size distributions of ambient cerium containing particles from fuel additives using modeling

Type: DATA
MODEL

Delivery Date (FY): 2016

(1) Develop and assess bioavailability tools for assessing human exposures to silver nanoparticles.

Type: OTHER

Delivery Date (FY): 2013

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)

NRMRL: Thabet Tolaymat, Souhail Al-Abed, Mark Mason, Kirk Scheckel, Todd Luxton, Anthony Zimmer NERL: HEASD: Kim Rogers, Karen Bradham; Michael Lewandowski.ERD: Dermont Bouchard, Nick Loux, Rajbir Parmar, Caroline Stevens, Quincy Teng, Candida West; ESD: Ed Heithmar AMAD: Kathleen Fahey, Havala Pye. NHEERL: David Thomas, Michael Hughes, Teresa Green, Karen Herbin-Davis, Brenda Edwards.

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Evaluate potential relationships between in vitro methods and preliminary Scheduled:

in vivo assays (mouse model).	Q4 - 2012 Completed:
(Product 1) Determine if in vitro methods are capable of predicting results from the mouse model.	Scheduled: Q2 - 2013 Completed:
(Product 2) Refine and evaluate high throughput techniques that use deep well plates packed with porous media coupled with analytical plate reader methods for the rapid determination of the transport potential of CNT through sand/sediment.	Scheduled: Q3 - 2012 Completed:
(Product 3) Provide data and relationships for models that describe the deposition of CNTs including effects of changing ionic and natural organic matter composition on attachment coefficients and critical coagulation coefficients	Scheduled: Q4 - 2012 Completed:
(Product 3) Provide report on data and relationships that can be used to predict the effects of CNT transformations on their deposition and coagulation.	Scheduled: Q4 - 2013 Completed:
(Product 4) Provide report on the microscopic characterization of ambient (Newcastle) and freshly-exhausted cerium-containing particles from diesel fuel additives.	Scheduled: Q2 - 2013 Completed:
(Product 4) Characterize the size and mixing state of ambient cerium-containing particles from fuel additives based on observations and modeling	Scheduled: Q4 - 2013 Completed:
(Product 4) Provide report on analysis of results from a field project in Newcastle UK on transport of nanoceria from diesel fuel.	Scheduled: Q4 - 2013 Completed:
(Product 5) Development of methods for characterizing the potential leaching of nano Cu from wood products.	Scheduled: Q4 - 2012 Completed:
(Product 5) Develop and evaluate an in vitro method for the determination of the potential bioavailability of CuNP.	Scheduled: Q4 - 2013 Completed:
(Product 6) Provide data and methods for characterizing metal (Ag and Cu) nanoparticles in wastewater treatment plant effluents	Scheduled: Q4 - 2012 Completed:
(Product 7) Provide experimental and modeling tools for evaluating the effects of changing polymer nanocomposite inherent chemical properties on environmental persistence.	Scheduled: Q3 - 2012 Completed:
(Product 7) Provide report on data and relationships for polymer CNT composites that can be used to predict polymer degradation rates and accompanying CNT release.	Scheduled: Q2 - 2013 Completed:
(Product 7) Provide report documenting the changes of inherent properties of nano materials in consumer products using computational chemistry with multi-scale models characterizing activation energy, band gaps, and bonding energy.	Scheduled: Q4 - 2012 Completed:
(Product 7) Provide report on the correlation between the mechanical and/or chemical transformation of nanomaterials from consumer products in the presence of environmental stressors and the resulting changes in inherent properties.	Scheduled: Q4 - 2013 Completed:

Division Approved Yes

CSS

Catalog and Link Chemical Profile to Models

CSS 131 131

Mace Barron
NHEERL
GED

Topic/Theme

1 Inherency

Project

1.3 Linking ICP to Metrics Relevant to Risk Characterization and Risk Management

Associated Project

None

Task Description

OCSPP is moving towards more integrated approaches to testing and assessment (IATA) for human health and ecological risk assessment of pesticides. With mechanistically-based Quantitative Structure-Activity Relationships (QSARs) being identified as an important component in meeting this goal under 40CFR158W, OCSPP proposed revised testing requirements for antimicrobial agents including a new optional guideline for submission of QSAR analyses. OCSPP has also proposed use of QSARs to fill data gaps, particularly for pesticide degradation products, where little or no empirical data are available from the registrant or via empirical data bases. Although reliable QSAR tools exist, most were developed in support of TSCA legislation and therefore do not include models that focus on adverse outcome pathways (AOPs) relevant to pesticide parent and/or degradation compounds. Since many of the pesticide active ingredients have a known molecular site of action for the target pest, an AOP approach will be used when developing the models, and will be supported by a taxonomically-based look-up tool for mode of action (MOA). This Task will also develop an MOA assignment methodology for ToxCast and other non-pesticide chemicals. New MOA-based QSAR models will be developed with goal of reducing uncertainty in toxicity estimation for a diversity of chemicals for application in OCSPP risk assessments and hazard screenings.

Rationale and Research Approach

Rationale: The development of acute MOA tools for estimating potency of pesticides and other chemicals in aquatic and terrestrial species is among the highest priority research needs of OCSPP. This work will deliver several high priority tools, including an MOA look-up tool for pesticides for OPP which will be expanded to include ToxCast chemicals. The research will also provide MOA-specific QSAR models to predict acute toxicity in aquatic and wildlife species. This work links to Systems Models by providing a searchable MOA database, and to Dashboards and Life Cycle Considerations by providing new MOA-based QSAR models for deployment. Approach: This cross-ORD collaboration with scientists from NCCT, NCEA, NERL, NHEERL, and NRMRL will apply their respective expertise and knowledge toward an integrated, transdisciplinary project by developing MOA based tools to support OCSPPs ecological risk assessments. The task will develop a database and lookup tool linking inherent chemical property (ICP) data to MOA information or biological activity, by major taxonomic groups. The task will also curate data for use in model development, and subsequently, develop and validate new predictive QSAR models and tools to fill existing and developing model gaps. The outputs from this research will allow application of ICP to future risk assessment needs, including the evaluation of chemicals and their potential alternatives from a molecular level in order to promote sustainability by reducing or eliminating the use and generation of hazardous substances. Modeling applications that will be developed in this project include a MOA look-up tool and mechanistically-based QSAR models focusing initially on pesticides but expanding to include other chemicals of priority to the Agency, including ToxCast compounds. Critical to the application of the approaches used in this effort, is having an understanding of the domain of applicability of these QSAR models, ICP information of the model sets, and the ability to identify chemicals that have similar

MOAs. The MOA look-up tool will be used to help assign MOAs for chemicals, expanding on the existing ASTER software. Further research will be initiated to identify how conserved the acute MOA is across selected taxonomic hierarchy. MOAs assignments will also be used to create more refined QSAR toxicity estimations. Once the MOA prediction models are validated, QSARs will be developed based on these specific MOAs with an initial focus on aquatic species but will later expanding to terrestrial species. These tools will be linked, via the CSS Dashboard, to EPA databases (e.g. ECOTOX, ToxRefDB) allowing risk assessors to estimate relative potency of pesticides and non-pesticides for the index of most sensitive species. This research effort will deliver tools that can be used in the evaluation of new chemicals, which can be used by OCSPP. Also, the models and tools developed here will feed into the tools developed within Life Cycle Considerations to improve their sustainability assessments.

Outputs from Projects related to this task

(1) Pesticide MOA profiling tool to OPP (2) Database of MOAs and assignment methodology to OCSPP (3) Improved MOA-based QSAR ecotoxicity models to OCSPP

Expected Products

(1) Version 1.0 of MOA look-up tool linking pesticide, ToxCast chemical ICP information, and MOA.

Type: DATA SOFTWARE

Delivery Date (FY): 2013

(2) Provide an improved MOA assignment methodology and expanded database of MOAs to OCSPP for use in risk assessments, linked to DSSTox chemical registry & searchable through ACToR by name, CAS, SMILES: a) compiled ecotox LC50 values b) compiled target and non-target pesticide specific MOAs c) assigned MOAs for ToxCast & other chemicals.

Type: DATA DATABASE

Delivery Date (FY): 2014

(3) Provide improved MOA-based QSAR ecotoxicity models to Dashboards.

Type: DATA MODEL

Delivery Date (FY): 2015

Start Date Q1 2012

End Date Q4 2015

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)

NCCT: Ann Richard NCEA: Nina Wang NHEERL: Chris Russom (MED): Crystal Jackson (GED); Mace Barron (GED) NERL: Rocky Goldsmith (HEASD) NRMRL: Todd Martin (STD); Doug Young (STD)

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Compile target and non-target pesticide specific MOAs	Scheduled: Q4 - 2012 Completed:
(Product 2) Develop MOA assignment methodology based on chemical structure	Scheduled: Q4 -

characteristics	2013 Completed:
(Product 2) Compile ecotox LC50 values for pesticides, ToxCast, and other chemicals	Scheduled: Q4 - 2013 Completed:
(Product 2) Assign MOAs	Scheduled: Q4 - 2013 Completed:
(Product 3) Develop MOA-specific QSAR models for acetylcholinesterase inhibitors, narcotics, reactives, neurotoxicants (pyrethroids, organochlorines)	Scheduled: Q4 - 2014 Completed:

Division Approved Yes

CSS

Develop ICP-Based Models

CSS 132 132

Rocky Goldsmith
NERL
HEASD

Topic/Theme

1 Inherency

Project

1.3 Linking ICP to Metrics Relevant to Risk Characterization and Risk Management

Associated Project

None

Task Description

This task focuses on the use of key inherent chemical properties (ICP) to develop tools and models necessary for understanding environmental fate/transport, absorption, distribution, metabolism and elimination (ADME) pharmacokinetics, and bio-molecular profiling in support of risk assessment. This task will provide guidance for developing, using and assessing the performance of ICP-based models to predict potential adverse outcomes and associated exposure-dose and fate metrics. The research is expected to improve workflows along a tiered enrichment process for molecular categorization and chemical prioritization by employing emerging software tools and ICP estimation models. Models and tools generated within this task will feed into data-streams for other CSS Topics (e.g., Systems Models, Life-Cycle Considerations, Biomarkers, Dashboards).

Rationale and Research Approach

Inherent chemical properties (ICP) place a chemical in the context of available biological and environmental data (e.g., exposure, toxicity, environmental fate) and within a group of related chemicals. Whereas individual physico-chemical properties of a substance may be useful in isolation (e.g., volatility can determine potential inhalation exposure), placing these properties within a group of related chemicals is more valuable for informing chemical design, hazard screening, risk assessment, and life-cycle assessment. ICP information is required to sort chemicals into relevant groups (e.g., chemical classes) in order to link sets of attributes with biological response variables. Efficient use of extant/historical data (Projects 1 and 2) requires chemoinformatic techniques such as data-mining and statistical tools to properly address the scope and limitations of existing data. The ability to apply data-mining tools to support data resources or data-streams is essential for evaluating the confidence of model predictions (such as for a new chemical) or for more broadly assessing the domain of applicability and model limitations. Models developed using this repository of ICP information shall be applied to individual chemicals and mixtures that could pose potential exposure or hazard risks. The ICP databases, models and assessment capabilities will provide information required to address outputs under other CSS research topic areas (e.g., Systems Models, Life-Cycle Considerations). The success of the research will depend on establishing links to endpoints/parameters required by the Agency to explain or address (or are used) in risk assessments. Much of this information exists within ORD, EPA, and published open literature, and can be mined from existing systems, but will need to be expanded to capture a larger universe of chemicals (e.g., industrial organics, pesticides, pharmaceuticals, nanomaterials). This task will utilize existing datasets and/or augment datasets as needed within Project 1. Chemoinformatic methods will be developed to build models from existing ICP data resources. These ICP-based models will be augmented by methods to assess confidence in predictions and identify data and model gaps. These capabilities can be incorporated into workflows to construct weight-of-evidence arguments, and support complex risk assessment models (e.g., PBPK, and fate and transport). The approach to completing this task is a four-fold tiered process: (1) Develop workflows to implement linkages between ICP and models. Guidance for developing, using and assessing the performance of ICP-based models shall be provided. General approaches on the use of

specific models and tools necessary to profile chemicals shall be developed. Approaches for developing models with ADME endpoints, physiologically-based pharmacokinetic (PBPK) parameters, and biomolecular interactions will be developed. [Products (3), (5) and (6)] (2) Develop tools to assess model performance. Many of the models and tools that have been developed for use in Agency risk assessment focus on limited chemical domains and may not be useful in diverse risk assessment scenarios. Prior extant models that have been developed for use in Agency risk assessment, such as the Exposure Related Dose Estimating Model (ERDEM), shall be augmented to increase chemical domains applicable to more diverse risk assessment scenarios. Key to implementing these tools across the various Program Offices is presenting various data and model results in a scientific context that builds on nearest neighbor/analog concepts and allows weighting of the evidence in constructing decision support arguments. An essential requirement is the ability to convey level of confidence in data and predictions for a particular chemical, and limitations of models and their applicability. Corollary requirements are the development of strategies for identifying data and model gaps for exposure and hazard endpoints, and knowing when simple vs. more complex models are required (i.e., value of information approaches). [Products (2), (5)] (3) Chemical profiling and categorization approaches for hazard and exposure screening. Chemicals shall be sorted based on chemical class (e.g., chlorinated phenols, organophosphates); chemical similarity (e.g., as used in US EPAs AIM or DSSTox structure-browser tools); chemical/molecular features, fragments, or spectral properties; molecular descriptor-based QSAR methods; and structure alerts such as those incorporated in rules-based systems used by ASTER, DEREK, and Toxtree. Molecular docking approaches shall be utilized to inform chemical profiling based on potential molecular interactions. [Products (2), (3), (4), (7)] (4) Integrate, augment and develop ICP-based models and tools. Systems Models (e.g., PBPK, exposure models) built under Projects 1 and 2, shall be expanded to cover a broader chemical space (e.g., pesticide active ingredients, nanomaterials) with links to biological and environmental endpoints (e.g., fate and transport of nanomaterials, formation of metabolites). Molecular descriptor based methods, i.e., such as hierarchical clustering or high-throughput screening (HTS) shall be used to develop QSAR models for broader data sets that contain a variety of chemical classes. Augmentation and integration of developed models with more complex system models will also be implemented. [Products (1), (3), (4), and (5)]

Outputs from Projects related to this task

(1) DockScreen: A resource of inherent chemical properties (ICP), molecular descriptors and selected biological activities for chemicals of interest to OCSPP. (2) Development of PReParE (Physiologically Relevant Parameter Estimation): A web-accessible (within EPA only [intranet]) in silico/knowledge based ADME (absorption-distribution-metabolism-elimination) resource in support of physiologically-based pharmacokinetic (PBPK) dosimetry models and exposure-dose extrapolation.

Expected Products

(1) Identify, curate and develop QSAR models into PReParE for predicting biotransformation for application in human health risk assessment with appropriate program office and ORD lab input/collaboration (PBPK models)

Type: DATA
MODEL

Delivery Date (FY): 2014

(7) Develop approaches for using and integrating molecular docking (in silico) techniques in rational chemical prioritization.

Type: OTHER

Delivery Date (FY): 2014

(2) Use of chemical space concepts to identify ADME database and model uncertainties and domains of applicability

Type: DATA
MODEL

Delivery Date (FY): 2014

(3) Use and develop Molecular Docking Approaches to Screen ToxCast Chemicals

Type: OTHER Delivery Date (FY): 2015

(4) Link QSAR models w/in PReParE to exposure-dose PBPK models on select case studies; characterize uncertainties and domain of applicability for QSAR models

Type: DATA
MODEL Delivery Date (FY): 2014

(5) Refine and augment PReParE - incorporate new models, identify domains of applicability and define the scope of the chemical space for developed models

Type: OTHER Delivery Date (FY): 2015

(6) Integrate and expand upon ADME database and models towards exposure based PBPK models, test exposure route scenarios, test route-to-route as well as species-to-species extrapolation.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2015

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NERL: Daniel Chang, Chris Grulke, John Kenneke, Chris Mazur, Rocky Goldsmith NCCT: James Rabinowitz, Stephen Little, Ann Richard, John Wambaugh NHEERL: Hisham El-Masri, William Lefew NCEA: Rob DeWoskin OCSPP: Niva Kramek (OCSPP)

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Identify and consolidate in vitro datasets for microsomal and hepatocyte clearance for man and animal surrogates (rats, mice, primates), in addition to data-sources for enzyme kinetics.	Scheduled: Q2 - 2012 Completed:
(Product 1) Identify links to open-access tools that can be used to enumerate putative downstream metabolic progeny of a parent chemical of interest.	Scheduled: Q3 - 2012 Completed:
(Product 1) QA chemical structures related to said data above	Scheduled: Q4 - 2012 Completed:
(Product 1) Calculate molecular descriptors using a variety of cheminformatics suites (i.e. MOE, OpenEye, etc&)	Scheduled: Q1 - 2013 Completed:
(Product 1) Develop a mathematical model that uses bond energy criteria, tissue specific expression criteria, major metabolic reaction sub-types and consensus modeling to prioritize metabolite formation	Scheduled: Q3 - 2013 Completed:
(Product 1) Integrate or link these models within PReParE for Web 2.0 parameter	Scheduled:

estimation	Q4 - 2013
	Completed:
(Product 1) Develop decision tree methods, and a variety of mining and machine learning approaches to estimate/bin/prioritize and categorize relative metabolic rate pools of parent chemical loss	Scheduled: Q2 - 2013
	Completed:
(Product 1) link data flow to ACToR	Scheduled: Q1 - 2014
	Completed:
(Product 2) descriptor comparison framework (i.e. physicochemical descriptors, topological descriptors, biomolecular interaction descriptors (from docking), and molecular fingerprints	Scheduled: Q1 - 2013
	Completed:
(Product 2) CHEMGPS (Chemical GPS) or PCA (principal component analysis) projection of different model training sets to see if models overlap, and in which chemical space we would expect to see confidence (i.e. distanc e metrics in chemical space)	Scheduled: Q3 - 2014
	Completed:
(Product 3) Identify databases of molecular docking output (i.e. ligand/protein interaction scores or energies) with associates ligand structures	Scheduled: Q4 - 2012
	Completed:
(Product 3) Consolidate in-house efforts on molecular docking using two main-stream molecular docking packages into a database and build a queryable user-interface for stakeholders and scientists alike	Scheduled: Q4 - 2013
	Completed:
(Product 3) Develop filter and/or constraint methods for prioritizing docking based on output of item 2	Scheduled: Q3 - 2014
	Completed:
(Product 3) Integrate within PReParE, and link data out to ACToR	Scheduled: Q2 - 2015
	Completed:
(Product 4) Identify all PBPK related parameter requirements	Scheduled: Q3 - 2013
	Completed:
(Product 4) Identify literature instance of models used for estimating PBPK-specific parameter and store databases of PBPK context queries	Scheduled: Q1 - 2014
	Completed:
(Product 4) Identify 3-5 examples of validated PBPK models where parameter estimation can be used to compare the final PBPK model output using newly derived parameters versus random-guess or nearest-neighbor approaches	Scheduled: Q3 - 2014
	Completed:
(Product 4) Identify model sensitivities to said parameters.	Scheduled: Q4 - 2014
	Completed:
(Product 5) Using approaches identified in Project 2 above Identify the Source-to-outcome location of a given model integrated within PReParE and identify open-access datasets/databases and opensource models for open-access workflows.	Scheduled: Q4 - 2013
	Completed:
(Product 5) Identify training sets or validation sets for these models	Scheduled: Q2 - 2014
	Completed:
(Product 5) In conjunction with Task 1.1.1, calculate appropriate metric (descriptors or PCA space from CHEMGPS reduced dimensionality representation) for assessing DOA overlap between models along the source to outcome continuum	Scheduled: Q4 - 2014
	Completed:

(Product 5) In conjunction with Task 1.1.1, provide A refined dataset of chemicals for which overlap between model DOA spaces exist (i.e. chemicals that define the chemical space for which one could integrate multiple models)	Scheduled: Q3 - 2015 Completed:
(Product 6) Link to Task 1.1.2 and consolidate ADME endoints into ACToR using models developed in Projects 1,4,5 and 7	Scheduled: Q3 - 2014 Completed:
(Product 6) Provide link to chemical structure in ACToR	Scheduled: Q1 - 2015 Completed:
(Product 6) Identify corpus of literature for chemical space related to inhalation, ingestion and skin absorptionand identify chemical spaces discrete to each.	Scheduled: Q3 - 2015 Completed:
(Product 6) Create molecular descriptor based machine-learning mined filters or rules-of thumb for estimating most likely route of ADME that could be easily integrated into a dashboard. For protein structure the analog is the Ramachandron plot, here a hyper-surface with topological delineation of different exposure routes disposition routes and elimination routes will be required.	Scheduled: Q1 - 2016 Completed:
(Product 6) For species-species extrapolation identify literature where allometric scaling has been used for species to species extrapolations, and compare how these new approaches for parameter estaimtion could be used for as many cases as possible. Identify a rational molecular basis for animal model selection beyond convenience based on putative biomolecular interactions and metabolites and sequence identity.	Scheduled: Q2 - 2016 Completed:
(Product 7) Identify use scenarios of integrating in silico-in vitroin vivo paradigm (i.e. correlation or enrichment, or insight?)	Scheduled: Q2 - 2012 Completed:
(Product 7) Communicate with shareholders that use in vitro and in vivo data for decisions-making and provide level of insight and confidence and molecular accountability of these methods.	Scheduled: Q4 - 2012 Completed:
(Product 7) Develop mock-up / wireframe of an interface that is amenable to query ligand/target or ligand/multi-target interactions for comparison or screening	Scheduled: Q4 - 2013 Completed:
(Product 7) Implement dashboard design for in silico (molecular docking) ligand/target surrogate data that allows re-call or queuing of priority chemicals for future docking studies.	Scheduled: Q1 - 2014 Completed:

Division Approved Yes

CSS AOP-Based Effects Monitoring and Exposure Reconstruction

CSS 212 212

Drew Ekman
NERL
ERD

Topic/Theme

2 Systems

Project

2.1 Systems-Level Approach to Adverse Outcome Pathway (AOP) Discovery and Application

Associated Project

None

Task Description

This task focuses on the application of pathway-based effects data (e.g.,omictools, medium- and high-throughput in vitro methods, and in vivo biomarkers), in conjunction with knowledge of adverse outcome pathways (AOPs), for effects-based monitoring and exposure reconstruction. Pathway-based effects data can complement the analytical monitoring tools used historically by EPA and thus aid Program Offices and Regions in addressing situations in which: (1) unknown(and hence unmeasured) chemicals may be responsible for adverse biological effects, (2) analytical detection limits may be inadequate with respect to biological effects, such as when transient exposures occur (i.e., the chemical is no longer present at detectable levels) that produce lasting biological effects, and (3) biological effects result from aggregate exposures (i.e., chemical mixtures). Anticipated applications of this research include monitoring impacted ecosystems such as Great Lakes Areas of Concern and assessing the progress of remediation efforts, particularly where the chemical(s) responsible for adverse effects are unknown or no longer detectable. In addition, since direct measure of exposure to environmental contaminants in real time (i.e., as the exposure is occurring) is rare and difficult to conduct, ORD clients are frequently faced with diagnosing or reconstructingpast exposures and establishing sufficient credible evidence to support criminal investigations and enforcement actions. This task is aimed at the development of effects-based monitoring tools and methods that support such applications.

Rationale and Research Approach

There are many chemicals of emerging concern(CECs) which are defined as such either because sensitive and specific analytical methods for detecting their occurrence in the environment or concerns over the types of effects they may cause have only recently emerged. Examples include potentially endocrine-active chemicals, pharmaceuticals and personal care products, flame retardants, perfluorinated chemicals, and presumably others yet to be identified. Application of quantitative structure activity relationships, high throughput toxicity pathway-based in vitro assays, genomics and other 21st centurytoxicity testing tools have the potential to provide hazard information for vast libraries of chemicals in a relatively rapid and cost effective manner. However, use of that information in risk assessment necessitates that complementary exposure information is available. Furthermore, in the context of sustainability, it also necessitates that exposures are considered not in isolation, but rather in aggregate. Exposure assessment has classically relied on instrumental and analytical monitoring of specific chemicals of concern. However, there are some well recognized limitations to these approaches relative to management/monitoring of large inventories of potential environmental contaminants as well as their associated degradates and metabolites. Among these limitations are those instances where unknown(and hence unmeasured) chemicals are responsible for adverse biological effects or when analytical detection limits may be inadequate with respect to biological effects. Additionally, uncertainty exists regarding the possible biological effects of complex chemical mixtures. Past regulatory/monitoring efforts have recognized these drawbacks and addressed them through the use of biological effects-based testing to complement chemical analyses. For example,

almost 20 years ago, the National Pollution Discharge Elimination System (NPDES) permitting program administered under the auspices of the Clean Water Act started to incorporate acute or chronic toxicity (e.g., effects on survival, growth, reproduction) limits into effluent permits. However, the types of methods and apical endpoints considered in such testing are inadequate to detect a range of effects of concern in 21st century risk assessments, including a variety of sublethal effects, potentially long-term or multi-generational effects, effects specific to sensitive subpopulations or life stages, etc. Consequently, there is a need for pathway-based effects monitoring approaches that employ the types of non-standard endpoints (e.g., targeted molecular and biochemical measurements anchored to specific toxicity/adverse outcome pathways; omics) currently being considered for hazard assessment and screening of individual chemicals. The intent would be to leverage the power of pathway-based effects monitoring to cast a broader netthan could be cost-effectively achieved using analytical methods, while at the same time increasing the specificity of the information associated with the effects data. Rather than simply identifying a non-specific toxic outcome, effects would be more directly anchored to specific molecular initiating events and an associated knowledge-base regarding the types of chemical structures able to cause the initiating molecular interaction, with much of that knowledge-base emanating from CSS research. In response to this need, this task aims to use a series of case studies that consider various exposure scenarios of relevance to Program Offices and Regions to demonstrate and develop the utility of effects-based data for monitoring and exposure reconstruction. Specifically, Product 1 will utilize pathway-based effects data collected from fish exposed in situ, as well as in the laboratory, to waste-water treatment plant discharges and/or agricultural runoff. These data will be interpreted in the context of analytical characterization of surface water contaminants at the same sites. This will provide a means to develop/evaluate the use of pathway-based effects tools for site characterization by using input regarding known contaminants at the sites as a first step in the progression of this approach. Further development/evaluation of pathway-based effects approaches will focus on the use of specific omics data (i.e., transcriptomics and metabolomics) with appropriate bioinformatic methods in order to assess progress of remediation efforts within Great Lakes Areas of Concern (Product 2) in support of the GLRI (high priority for GLNPO/Region 5). These omics technologies have been found to be particularly sensitive with respect to temporal changes occurring in impacted organisms, potentially allowing the nature and severity of impairment to be tracked over the duration of remediation efforts. Similar to Product 1, this product will involve the use of fish deployed to selected sites. Site selection will be carried out in coordination with input from GLNPO/Region 5. Case studies associated with Product 2 will serve to inform the development of recommendations regarding the use of omics for effects-based monitoring in aquatic environments. Mechanism based in vitro bioassays represent another type of biological effects-based tool that can be used to screen environmental samples for specific types of biological activity linked to adverse outcomes of concern. As such assays are automated for high throughput using robotics and computational approaches, they offer a means to characterize effects of environmental samples in an efficient and cost effective manner while reducing animal use. However, in order to properly develop and apply these methods, determination of best practices for preparation of environmental samples for in vitro exposures is necessary. Product 3 will respond to this need by testing/validating various methods for collection, storage, and transportation of surface waters from selected sites. Similar to Products 1 and 2, case studies aligned with high priorities to the Program Offices and Regions will be selected. While research aligned with products 1-3 will focus largely on effect-based monitoring, research associated with Products 4 and 5 focus on exposure reconstruction applications including determination of the causal agents in complex mixtures. Specifically, Product 4 will employ laboratory-controlled case studies to evaluate whether pathway perturbation motifs (patterns of biological response) are conserved for individual chemicals when those chemicals are present in complex mixtures. The results of this approach will aid assessment of feasibility, optimization of analytical approaches, and facilitate development of recommendations regarding the use of pathway-based approaches (including omics) for assessing exposures to multiple stressors. While Product 4 utilizes a controlled laboratory setting to test specific hypotheses and assumptions underlying the use of pathway-based tools for identifying causal agents in complex mixtures and exposure reconstruction, Product 5 will be aimed at applying these approaches for various surface waters including the Great Lakes (high priority for GLNPO/Region 5), arid western rivers (high priority for Region 8), or heavily impacted eastern receiving waters known to produce significant adverse effects in fish such as increased incidence of the intersex condition (high priority for Region 3). The aim of these case studies

will be to develop and optimize pathway-based exposure reconstruction methods for real world environments. Such tools would assist Program Offices such as The National Enforcement and Investigation Center (NEIC) and the Regions in reconstructing past exposures. Information of this nature may be critical when conducting criminal investigations and for supporting enforcement actions where both the identification of the causal agent and the establishment of a timeline of events are required. Finally, it is recognized that potential population and ecosystem-level impacts are the primary drivers of ecological risk management decisions. Therefore, a portion of this task will focus on utilizing effects-based monitoring data as a basis for forecasting potential population impacts. Specifically, product 6 focuses on the development of a model construct for forecasting changes in fish population status using pathway-based effects data anchored to key events in reproductive adverse outcome pathways.

Outputs from Projects related to this task

(1) Methods for integrating pathway-based effects data into monitoring strategies for assessing contaminated or remediated sites of interest to the Program Offices and Regions. (2) Best practices for the collection, storage, and transportation of surface waters for use in mechanism-based in vitro bioassays. These bioassays are intended for use in the screening of environmental samples for specific types of biological activity linked to adverse outcomes of concern of significance to the Program Offices and Regions. (3) Recommendations regarding incorporation of pathway-based effects monitoring into exposure reconstruction strategies that Program Offices and Regions use in conducting assessments and investigations of impacted waters.

Expected Products

(1) Case study on use of pathway-based effects data for exposure characterization: Using pathway-based effects in fish to characterize exposures associated with waste-water treatment plant discharges and/or agricultural runoff. Comparison to analytical characterization of surface water contaminants will be conducted for select sites. This case study is responding to needs from Regions 3, 5 and 8.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2012

(2) Case studies evaluating the utility of transcriptomics, metabolomics, and associated bioinformatic methods for comparing the nature and severity of biological impairment as a function of space and/or time to assess the efficacy of remediation efforts within Great Lakes Areas of Concern.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(3) Best practices for preparation of surface water samples for in vitro analyses using pathway-based assays, including high throughput assays.

Type: OTHER

Delivery Date (FY): 2014

(4) Peer-reviewed case studies evaluating conservation of pathway perturbation motifs elicited by an individual chemical with those elicited following exposure to the same chemical when present in a complex mixture. Results will aid development of recommendations regarding the use of pathway-based biological responses and/or 'omics' for multiple stressor assessments.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(5) Develop methods for applying pathway-based effects data (in vitro and/or biomarker) from genomics, and AOP knowledge to identify putative causal agents for chemical mixtures from surface waters like the Great Lakes (Region 5, GLNPO), arid western rivers (Region 8), or heavily impacted eastern receiving waters (Region 3). These methods will also be developed in coordination with The National Enforcement and Investigation Center (NEIC) in support of biomonitoring/exposure

reconstruction tools for potential application to Agency criminal investigations and enforcement actions.

Type: OTHER Delivery Date (FY): 2015

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NHEERL: Villeneuve, Ankley, LaLone, Miller, Jensen, Kahl, Durhan, Makynen NERL: Ekman, Collette, Skelton, Teng

External Collaborators (known or proposed)

TBD

Milestones

(Product 1/2) Peer reviewed manuscript(s) and/or report(s) describing the outcomes of the multiple site (AOCs) test study mentioned above.	Scheduled: Q4 - 2013 Completed:
(Product 1/2) Linkage of pathway-based effects data (determined through the case studies mentioned above) to relevant adverse outcomes for development of AOPs. [Outyears]	Scheduled: Q4 - 2016 Completed:
(Product 3) Survey current practices by consulting in-house experience (ORD, Program Offices, Regions, etc.) and the scientific literature.	Scheduled: Q4 - 2013 Completed:
(Product 3) Evaluate promising approaches using simple (i.e., fewer samples, easily accessible sampling sites, limited number of assays, etc.) case study.	Scheduled: Q2 - 2014 Completed:
(Product 3) Conduct larger scale proof of concept case study (multiple sites, larger number of assays, including high through-put) to assess limits of approaches. [Outyears]	Scheduled: Q4 - 2016 Completed:
(Product 3) Manuscript and/or report on selection and validation of best practices approach for surface water sampling. [Outyears]	Scheduled: Q4 - 2016 Completed:
(Product 3) Offer recommendations (including a decision tree if different approaches appear better suited for different applications) regarding best practices for surface water collection, storage, and transportation to Program Offices and Regions. [Outyears]	Scheduled: Q4 - 2016 Completed:
(Product 4/5) Conduct case studies to evaluate the extent to which pathway perturbations are conserved for individual chemicals when those chemicals are present in complex mixtures.	Scheduled: Q4 - 2012 Completed:
(Product 4/5) Perform case study designed to assess use of pathway-based effects in reconstructing simple (limited number of chemicals, short exposure duration, etc.) exposures. [Outyears]	Scheduled: Q4 - 2016 Completed:
(Product 4/5) Conduct relatively complex case study to more extensively test the potential of using pathway-based effects for exposure reconstruction. [Outyears]	Scheduled: Q4 - 2016 Completed:

(Product 4/5) Peer reviewed manuscript and/or report evaluating the potential for using pathway-based effects in conducting exposure reconstructions. [Outyears]	Scheduled: Q4 - 2016 Completed:
(Product 4/5) In situ evaluation of the approach conducted through collaborations with Program Offices and Regions. [Outyears]	Scheduled: Q4 - 2016 Completed:
(Product 1/2) Survey current practices by consulting in-house experience (ORD, Program Offices, Regions, etc.) and the scientific literature.	Scheduled: Q2 - 2012 Completed:
(Product 1/2) Conduct parallel in situ studies at multiple Areas of Concern (AOCs) using the lessons learned in the pilot study.	Scheduled: Q2 - 2013 Completed:
(Product 1/2) Peer reviewed manuscript(s) describing the outcomes of the pilot study mentioned above.	Scheduled: Q4 - 2012 Completed:

Division Approved Yes

CSS

Adverse Outcome Pathway (AOP) Discovery and Definition

CSS 211 211

Dan Villeneuve
NHEERL
MED

Topic/Theme

2 Systems

Project

2.1 Systems-Level Approach to Adverse Outcome Pathway (AOP) Discovery and Application

Associated Project

None

Task Description

The use of mechanistic or pathway-based data (e.g., QSARs, in vitro, biomarkers) in risk assessment and regulatory applications is limited by the lack of well-established linkages between endpoints measured, or predicted, at molecular and cellular levels of organization and adverse outcomes that manifest at higher levels of biological organization (e.g., organ function in humans; survival, growth/development, and reproduction in wildlife). In their vision and strategy for toxicity testing in the 21st century, the National Research Council cited the linkage of adverse effects to specific toxicity pathways (i.e., development of AOPs) as a critical research activity to support development and regulatory application of pathway-based testing. Research under this task is aimed at formalizing and expanding the description, inference, and dissemination of AOPs and AOP knowledge through a systems-level approach that identifies critical molecular interactions that initiate biological perturbation and links those perturbations to adverse outcomes at levels of biological organization relevant to risk assessment. The primary outcome of this research will be the population and annotation of an AOP knowledge-base (e.g., Effectopedia) with both new and existing AOP knowledge. Initial efforts will focus on AOPs relevant to reproductive and developmental toxicity in fish and the application of AOP knowledge to support hazard extrapolation across taxa.

Rationale and Research Approach

Research aimed at elucidating adverse outcome pathways (AOPs) provides a scientific foundation to address a number of critical challenges outlined in the CSS framework. These include: (1) identification of critical pathways perturbed by environmental chemicals that lead to adverse effects (p. 12); (2) ways to apply the knowledge gained in human health risk assessment to ecotoxicology(p. 14); and (3) enhancing interpretation of biomarkers. However, while there is a long history of research relevant to the elucidation of AOPs, well defined systematic approaches to the discovery, definition, and dissemination of AOP knowledge to regulators and other environmental decision-makers have been lacking. This research will be aimed at addressing those needs. We propose to employ a multi-step approach to AOP discovery and definition. The first step involves scoping the problem with relevant program office partners. For example, identifying a specific guideline toxicity test for which it would be desirable to develop more cost effective/efficient alternatives or developing an AOP relevant to a specific pesticide registration, water quality criteria development, etc. Once the scope has been defined the second step is to assemble the relevant expertise within ORD and/or via external partners and develop a conceptual model of the system of interest which includes critical biological functions and their regulation at the molecular level (to the extent it is understood). The conceptual model is then used to identify points/targets within the system that are potentially vulnerable to perturbation by the chemical(s) of interest. This assessment of putative molecular initiating events serves as the basis for hypothesized AOP formulation. Hypothesized AOPs are first evaluated against the extant literature to identify whether sufficient supporting evidence linking the molecular perturbation with an adverse outcome relevant to the regulatory context exists. Where gaps are identified or supporting evidence is lacking, targeted research is then conducted to fill data gaps, generate supporting evidence, and/or

reject the hypothesized AOP. Where feasible, this targeted research will employ omicapproaches (e.g., transcriptomics, metabolomics, proteomics) which will facilitate and accelerate the discovery of other biological pathways/functions impacted by chemical perturbations and provide important insights into the function of AOPs within a broader systems biology context. Once supporting information for an AOP has been generated and/or assembled, that information will then be deposited into a curated, accessible, searchable, and adaptable AOP knowledge-base (e.g., Effectopedia). The first product of this research program (Product 1) will involve working with relevant partners (e.g, World Health Organization Mode of Action steering committee, OECD, Effectopedia developers, ILSI-HESI) to develop a standardized template and format for the AOP descriptions that will be used to populate such an AOP knowledge-base. ORD scientists will also engage with program office partners to define AOP quality criteria that can be used to tag information in the knowledge-base relative to its suitability for various types of EPA applications. In addition to populating the AOP knowledge-base, aspects of this research will develop tools and approaches for evaluating the conservation of AOPs across taxa. These will be used to evaluate whether key molecular targets are conserved, whether they respond similarly to chemical perturbation, and to understand how differences in the conservation and/or physiological roles of those targets among taxa may influence both the susceptibility to adverse outcomes and the type(s) of adverse outcomes that occur in different taxa as a result of chemical exposure. This will facilitate annotation of that AOP knowledge-base with relevant information regarding the taxonomic domain of applicability for each AOP. Products 2 and 3 will focus on these aims. Product 2 will use iterative targeted testing approaches to evaluate comparability of AOPs and responses between fish, rodent, and potentially invertebrate models. Product 3 will consist of a web-based tool which will provide quantitative characterization of the molecular conservation of any protein target of interest among a diversity of taxa which may be relevant to a risk management decision. Finally, as AOPs are developed, the investigators will also identify specific QSAR, toxicity pathway assays (e.g., in vitro, high throughput assays), targeted tests and/or biomarkers with scientifically defensible relevance to specific adverse outcomes. This information will be mapped into the AOP knowledge-base to serve as a resource for identifying data that could be useful for assessments concerning a particular AOP (Product 4). Initial research under this task will build on established efforts within ORD related to the development of AOPs for reproductive toxicity and developmental neurotoxicity in small fish models. Consequently, the initial AOPs developed are expected to have relevance to the evolution of the Endocrine Disruptor Screening Program (e.g., EDSP21), identification of potential alternatives to fish early life stage toxicity tests (e.g., OCSPP 850.1400), and/or potential use of fish data for predicting developmental neurotoxicity in mammals (in support of OPPs Targeted Testing and Priority Setting workplans). However, as the research program evolves, the intent is for this line of research to mature into an active partnership between CSS scientists and risk assessors within specific program offices. The aim is to develop an efficient process whereby the programs can obtain ORD support in developing and/or applying AOP knowledge in support of specific program office activities. For example, to support an OPP ruling under FIFRA, points of contact within ORD could recruit CSS scientists with scientific expertise relevant to endpoints of concern identified for a chemical in question. These scientists would work with the OPP risk assessor to map the toxicity data submitted by the registrant to existing AOPs in the AOP knowledgebase and/or to develop new AOPs as needed. Critical data gaps identified through this process would be candidates for research under the experimental arm of this task. Over the course of these interactions, CSS scientists will work with the program office partners to develop a series of best-practices recommendations regarding the use of pathway-based data (e.g., in silico, in vitro, omics, and/or biomarkers), in conjunction with the AOP knowledge-base, to support the prediction of reproductive or developmental hazards associated with chemical exposures (Product 5).

Outputs from Projects related to this task

(1) Population of an AOP knowledge-base (Effectopedia) with multiple AOPs relevant to reproductive and developmental toxicity in fish, including AOP descriptions with supporting scientific evidence, evaluation of the taxonomic domain of applicability of the AOP, and identification of alternative data sources with potential utility for assessments related to the AOP. (2) A web-based tool which will provide quantitative characterization of the molecular conservation of any protein target of interest among a diversity of taxa. This tool will be used to inform predictions of which species are likely to be susceptible to adverse effects mediated through defined molecular initiating events as a means to

prioritize testing, guide cross-species extrapolation of data, and/or inform risk management decisions. (3) Established partnerships with interested program offices to provide ORD support for the mapping of toxicity data to relevant AOPs in the AOP knowledge-base or development of new AOPs as needed.

Expected Products

(2) AOP descriptions comparing linkages (e.g., causal) between specific pathway perturbations and reproductive or developmental outcomes in multiple species (e.g., rodents, fish, invertebrates) (reports). These will provide data that support the development of tools and guidance cross-species extrapolation of effects and hazard.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(1) A searchable AOP knowledgebase: Step 1) A standardized template for identifying key contents and format of the AOP descriptions that can be used to populate a searchable AOP knowledgebase. The product will include several example AOPs descriptions for reproductive toxicity and developmental neurotoxicity with immediate relevance to EDSP21 and Priority Setting workplans developed with OCSPP and OW.

Type: DATA
DATABASE

Delivery Date (FY): 2013

(3) Web-based tool for evaluating cross-species conservation of key molecular targets associated with molecular initiating events and/or key events represented in AOPs as a means for predicting the relative sensitivity or susceptibility of various species to adverse effects associated with exposure to chemicals acting through those AOPs .

Type: DATA
SOFTWARE

Delivery Date (FY): 2014

(4) Annotation of an AOP knowledge-base with information identifying specific QSARs (e.g., those being developed under the Inherency Topic), pathway-based in vitro assays (including high throughput), and medium throughput in vivo endpoints (e.g., with fish embryo assays, biomarkers, metabolite changes) relevant to specific AOPs for reproductive or developmental toxicity.

Type: DATA
DATABASE

Delivery Date (FY): 2016

(5) Recommendations regarding the use of pathway-based data (e.g., in silico, in vitro, omics, and/or biomarkers), in the context of an AOP knowledge-base, to predict chemical reproductive or developmental hazards in support of risk assessment.

Type: OTHER

Delivery Date (FY): 2016

Start Date Q1 2012

End Date Q4 2016

Cross Research Project Output Supported?
Maybe

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)

NHEERL: Villeneuve, Ankley, LaLone, Miller, Jensen, Kahl, Durhan, Makynen, Moser, Hartig,

External Collaborators (known or proposed)

TBD

Padilla, Edwards NERL: Ekman, Collette, Skelton,
Teng NCCT: Judson, Knudsen NCEA: Burgoon

Milestones

(Product 1) Participation in multi-stake holder meeting(s) regarding development of a standardized template and format for AOP descriptions and their submission to an AOP knowledge-based (e.g., Effectopedia).	Scheduled: Q4 - 2012 Completed:
(Product 1) Develop several prototype AOP descriptions related to reproductive toxicity and developmental neurotoxicity in fish and refine AOP description template/format as needed based on this experiment (with stakeholder input).	Scheduled: Q2 - 2012 Completed:
(Product 1) Author/co-author a manuscript or report describing the standardized AOP description template/format for use in populating an AOP knowledge-base (e.g., Effectopedia).	Scheduled: Q4 - 2012 Completed:
(Product 2) Conduct experiments allowing for comparison of AOPs and responses between fish, rodent, and potentially invertebrate models.	Scheduled: Q4 - 2012 Completed:
(Product 2) Conduct targeted experiments aimed at testing hypothesized AOPs and/or filling specific data gaps.	Scheduled: Q2 - 2013 Completed:
(Product 2) Peer reviewed manuscript(s) evaluating comparability of AOPs and responses between fish, rodent, and potentially invertebrate models [Product 2]. These studies will be used to help understand the taxonomic applicability domain of specific AOPs.	Scheduled: Q4 - 2013 Completed:
(Product 2) Peer reviewed manuscript(s) reporting on targeted and toxicogenomic experiments aimed at evaluation of hypothesized AOPs and filling data gaps. Outyears.	Scheduled: Q4 - 2016 Completed:
(Product 3) Presentation of prototype tools and dashboard to program offices and solicitation of program office input regarding functions, features, and interface desired in the final tool.	Scheduled: Q2 - 2012 Completed:
(Product 3) Case study evaluating the effectiveness of quantitative metrics of molecular target conservation for predicting species susceptibility to adverse reproductive impacts of a human pharmaceutical. Outyears.	Scheduled: Q4 - 2016 Completed:
(Product 3) Peer reviewed manuscript reporting on the final web-based general user version of the tool incorporating the functions, features, and interface characteristics requested by program office partners, along with concurrent delivery of the tool to the program offices. Outyears.	Scheduled: Q4 - 2016 Completed:
(Product 4) Map ToxCast and Tox21 assays, known QSARs, and other toxicity pathway assays (e.g., in vitro assays from EDSP, etc) to associated targets known to play important roles in development/reproduction.	Scheduled: Q4 - 2013 Completed:
(Product 5) Pilot collaboration with OPP and/or other program offices aimed at mapping of data to AOPs or development of new AOPs related to program office activities (e.g., pesticide registration, water quality criteria development, etc.).	Scheduled: Q4 - 2016 Completed:
(Product 5) Conduct targeted experiments aimed at testing hypothesized AOPs and/or filling specific data gaps.	Scheduled: Q2 - 2013 Completed:
(Product 5) Peer reviewed manuscript(s) reporting on targeted and toxicogenomic experiments aimed at evaluation of hypothesized AOPs and filling data gaps. Outyears.	Scheduled: Q4 - 2016 Completed:
(Product 5) Publication of best-practices recommendations regarding the use of	Scheduled:

pathway-based data (e.g., in silico, in vitro, omics, and/or biomarkers), in conjunction with the AOP knowledge-base, to support specific program office activities [Product 5] Outyears.	Q4 - 2016 Completed:
(Product 4) Use available data to conduct post-hoc analyses evaluating whether screening assay results were predictive of outcomes associated with specific AOPs related to reproductive or developmental toxicity. Outyears.	Scheduled: Q4 - 2016 Completed:
(Product 4) Mapping of specific QSAR, toxicity pathway assays (e.g., in vitro, high throughput assays), targeted tests and/or biomarkers with scientifically defensible relevance to specific adverse outcomes into the AOP knowledge-base [Product 4]. This is expected to be an on-going activity that will interface with multiple other CSS topics (e.g., Inherency, Biomarkers, other projects within Systems Models). Outyears.	Scheduled: Q4 - 2016 Completed:
(Product 5) Participation in multi-stake holder meeting(s) regarding development of a standardized template and format for AOP descriptions and their submission to an AOP knowledge-based (e.g., Effectopedia)	Scheduled: Q4 - 2012 Completed:

Division Approved Yes

CSS

Data Collection and Computational Modeling for the "Virtual Embryo"

CSS 222 222

Tom Knudsen
NCCT
IO

Topic/Theme

2 Systems

Project

2.2 Systems Modeling of Specific Tissues and Multi-Organ Pathways

Associated Project

None

Task Description

This task is focused on the predictive toxicology of childrens health and development following prenatal or lactational exposure to environmental chemicals. The research is motivated by a computational framework of developmental toxicity that will formally guide the generation, assessment and evaluation of data, tools and approaches focused on embryonic growth, morphogenesis and differentiation. The outcomes of the research will be improved understanding of the molecular pathways and cellular processes leading to adverse pregnancy outcomes and better ways to assess the impacts of prenatal and postnatal exposure to chemicals at various stages of development and scales of biological organization.

Rationale and Research Approach

The developing embryo is a complex adaptive system in which the susceptibility or resilience to chemical disruption varies by organ system and stage. The individual molecules and cells have their own developmental trajectories and form complex networks of interactions that regulate morphogenesis and differentiation. Whereas genetic approaches have identified these critical pathways, little is known about the pathways of toxicity leading to adverse developmental outcomes. Biomechanical forces, signaling gradients and genetic oscillations that pattern the embryo act with remarkable precision (robustness) but also must react quickly to perturbation (flexibility). The combination of robustness and flexibility is characteristic of an adaptive system at the edge of chaos. Task 2.2.2 aims to build computational models of development that can be used to analyze these complex interactions and predict chemical interactions with core functions such as molecular clocks, spatial gradients, molecular machines, growth mechanics and differentiation pathways. We propose that an array of Virtual Embryo models representing key aspects of embryonic development will effectively capture the flow of molecular information across discrete cellular networks and simulate mechanistic relationships leading to adverse developmental outcomes. To test this hypothesis, Task 2.2.2 will build cell-based computer models that simulate a morphogenetic series of events (e.g., blood vessel development, limb-bud morphogenesis, neural differentiation). The models will be hypothesis-based and incorporate vast information from the literature and HTS data from ToxCast to simulate emergent systems-level behaviors. The simulations will be qualified against experimental data and the models deployed for toxicological assessment. To do this, we propose a cell-agent based model (ABM) approach in which every cell is capable of autonomous decisions. Each simulated cell, like a biological cell, processes local cues from its environment and behaves according to its own blueprint or history. Higher-order responses of the system emerge from the collective cellular behavior in the simulation. This type of model is ideal for predictive toxicology because it integrates information across different biological scales: molecular information such as internal clocks, biochemical gradients, and gene regulatory networks; cellular properties such as growth, adhesion, and differentiation; and tissue-level properties such as homeostasis, morphogenesis, and repair. The cell-agent-based models in Virtual Embryo will be run from a computer program coding using the Python and XML scripting languages. Specific rules for molecular pathways and cellular behaviors are captured from intramural and extramural scientific literature in a virtual tissue knowledgebase (VT-KB), and the software to

implement multicellular interactions is an open access tissue simulation environment [http://www.compucell3d.org/]. Experimental data to profile the consequences of chemical exposure will be collected using assays with targets specific to developmentally important adverse outcome pathways (AOPs). Research to identify important toxicity pathways, develop assays to evaluate those pathways, and link in vitro signatures to phenotype will be conducted. For example, a phenotype integral to proper embryogenesis is vascular development, and disruption of that process can have serious developmental consequences. Because the pathways active in angiogenesis are similar across vertebrates it is possible to use an alternative species (zebrafish) to define the chemical effects on the process, thereby providing experimental data for profiling the consequences of chemical exposures. Furthermore, targets in angiogenesis pathways can be identified via an -omics approach for the identification of diagnostic biomarkers to facilitate model development and prioritizing chemicals based on modes of action. A life-stage based risk assessment paradigm requires information on absorption, distribution, metabolism and excretion (ADME) and unique life-stage and/or species susceptibilities that can be attributed to maternal-fetal exchange. There is a paucity of experimental data regarding the placental and lactational transfer of chemicals from mother to infant. We not know how or where the lipids come from that are present in breast milk, and even less is known about how xenobiotics partition into these lipids. Research to reduce uncertainty regarding the role of maternal body burden and depuration will develop cell-based in vitro models to better characterize and define these exposure pathways. For example, novel lipid-producing cells that model the mammary epithelium will be used to determine ADME, kinetic, and dosimetry parameters with respect to chemical storage, release and partitioning. In conjunction with this cell-based approach, research will be conducted to experimentally measure and develop a predictive model for determining partition coefficients for non-volatile compounds in breast milk and blood, which will facilitate the utilization of available biomonitoring data to predict potential infant exposures. We will then develop a physiologically-based model for predicting the concentration and distribution of foreign chemicals in breast milk to aid in life-stage specific exposure estimation and chemical risk assessment. Impact. Task 2.2.2 will provide a framework for ultimately translating results into regulatory context and computational models for using this information toward life-stage based risk assessment. These models will enable partners, clients and stakeholders to look globally at prenatal development in a new way, supporting predictive toxicology of growth, morphogenesis and differentiation. Reliance of the current paradigm on costly and lengthy animal testing, as well as uncertainties in extrapolating across species and maternal factors, cannot keep pace with increasing demands to evaluate new and existing chemicals and mixtures for developmental effects. In the near term, the proposed research will contribute to an integrated strategy that brings together tools and approaches in computational toxicology with systems biology to identify developmental hazards (based on relevant pathways of toxicity) and assess potency within the context of exposure information. In the longer term these results will be utilized to support the development of life-stage specific in silico virtual tissue/organ models that can replace current testing requirements and inform the development of high-throughput assays and risk management decisions. This approach directly supports Program Office needs, as well as EPA Administrator Jacksons principles for chemical reform including HTS, the development of in silico virtual tissue/organ models, and life-stage susceptibility analysis.

Outputs from Projects related to this task

(1) Computer models to predict effects on fetal development after maternal chemical exposure: Virtual embryo research integrates important data and scientific knowledge into sophisticated computer models that will simulate and predict what might happen to fetal development when the mother is exposed to different chemicals. We want to simulate what happens when developing systems are exposed to environmental chemicals. In the lab we can study smaller pieces of a process (e.g., angiogenesis or neurogenesis) and feed results into computer models to reconstruct the whole process. This requires small working prototypes in which autonomous cellular behaviors are linked to a microcosm of biological networks and multicellular interactions. To find out what could happen following different exposure scenarios, we would feed HTS data such as ToxCast or other in vitro data into the computer model and evaluate predicted developmental phenotypes. Running a number of simulations can show the range of predicted effects and reveal the earliest signs of adversity. Modeling the virtuome across dose-time-stage-species can inform targeted experiments to capture detailed cellular information (e.g., imaging, omics) and validate/refine the virtual proto-embryo. (2)

Delineating pathways of exposure and mechanisms of developmental toxicity using the virtual embryo for risk assessment: The predictions of virtual embryo simulations can be used to understand and test mechanisms of developmental toxicity across different doses, species and life stages. This understanding can provide guidance for life-stage specific targeted research to delineate pathways of exposure and mechanisms in both the fetus and infant. Computational modeling can lead to novel hypotheses about how inferences from in vitro data may propagate into key events leading to adverse pregnancy outcomes. These hypotheses can formally guide experiments that aim to generate data at a systems level, assess model performance, and refine the virtual tissue models. In this way we can ground the concepts, principles and possible solutions used for virtual model development in results from actual experimentation. (3) An integrated strategy for life-stage specific risk assessment: The outcomes of the research will lead to improved understanding of the molecular pathways and cellular processes underlying adverse pregnancy outcomes and better ways to assess the impacts of prenatal and postnatal exposure to chemicals at various stages of development and scales of biological organization. Toward an integrated strategy for life-stage specific risk assessment, the outcomes of the research will lead to improved understanding of the molecular pathways and cellular processes underlying adverse pregnancy outcomes and the integration of effects-exposure information. This will lead to better ways to assess the impacts of prenatal and postnatal exposure to chemicals at various stages of development and scales of biological organization.

Expected Products

(1) Integration of angiogenesis information: A cell-agent based systems model developed from empirical data and biological knowledge of blood vessel development. The angiogenesis model will be trained with compounds showing anti-angiogenic properties, assessed in a forward validation for predictive developmental toxicity among 1,000+ ToxCast chemicals in pregnant rats/rabbits, and tested for vascular disruption in zebrafish embryos and embryonic stem cell assays for 30+ chemicals in EDSP21/TSCA21/OW21/OPP21.

Type: DATA
MODEL

Delivery Date (FY): 2012

(2) Implementation of cell-agent based models linked to complex embryological phenomena (limb-bud morphogenesis, reproductive tract development). This product will deliver computer models imputing knowledge of signaling networks, tissue induction, spatial patterning, and molecular clocks to recapitulate morphogenesis and predict points of departure for dysmorphogenesis. The models would be trained with 20 reference compounds in ToxCast and applied to 20 data-poor chemicals in TSCA21.

Type: DATA
MODEL

Delivery Date (FY): 2013

(3) Stem cell differentiation and zebrafish embryogenesis: Data generation and functional analysis of AOP descriptions for phenotypic assessment of altered gene function. This product will provide HCS data to experimentally anchor specific toxicity pathways to developmental events for integration into predictive virtual tissue models of developmental processes and toxicities.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(4) Experimental ADME data and kinetic models that better predict prenatal (trans-placental) and neonatal (trans-lactational) exposure pathways. This product can be used to interpret maternal biomonitoring data and advance public health efforts to understand environmentally-induced infant mortality and morbidity.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(5) Expansion and integration of the Virtual Embryo toolbox. This product will plug-in other key

systems to the toolbox, including neural crest and somite development. Information from in silico models will be corroborated by in vitro work (stem cells, zebrafish and Xenopus embryos, cultured organs) and targeted in vivo studies. Product development will be guided by cell-agent based models and cell-imaging data, and implemented for 10 chemicals in EDSP21/TSCA21 with relevant activities in ToxCast.

Type: DATA
SOFTWARE

Delivery Date (FY): 2015

6) Integration of virtual tissue models into the virtual embryo model. This product will link modular virtual tissue models into an integrated testing platform for developmental toxicity (e.g., combining blood vessel development with limb-morphogenesis). It will emerge from iterative collaboration between computational modelers and laboratory investigators to provide experimental data supporting the principles, concepts, and possible solutions of in silico virtual tissues for predictive toxicology.

Type: DATA
MODEL

Delivery Date (FY): 2016

(7) Models that integrate exposure with effects through metabolic transformation, distribution, and chemical-chemical interactions as related to susceptible populations (e.g., physiologically-based compartment models for predicting the concentration of foreign chemicals in breast milk). This product will aid in lifestage-specific exposure estimation and reconstruction, and chemical risk assessment.

Type: DATA
MODEL

Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)

NCCT: T Knudsen, N Sipes, N Kleinstreuer, W Setzer NHEER/ISTD: S Hunter, K Chandler, S Jeffay, H Nicols, M Hoopes, M Rosen, S Padilla, T Tal, D Hunter, B Padnos, J Olin, K Jensen, W Mundy, T Freudenrich, T Shafer, K Wallace, H El-Masri, W LeFew, L Adams, J Royland, A Tennant, E Hunter, S Warren NHEERL/MED: [participant w/o FTE for FY12: S Degitz] NHEERL/GED: M Hemmer, K Salinas, P Harris, S Vickery, J Fournie, F Blue NHEERL/TAD: K Jensen, P Philips, R MacPhail, V Moser, [participant w/o FTE for FY12: C Lau, B Abbott, M Narotsky] NERL: J Kenneke, S Marchitti, [participant w/o FTE for FY12: C Mazur] Other Internal collaborators: Office of Childrens Health Programs (OCHP), Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Water (OW), Scientific Advisory Board (SAB)

External Collaborators (known or proposed)

Academic: STAR Co-ops with the Texas-Indiana Virtual STAR Center (U Houston, U Texas-Austin, Indiana U) [EPA-G2008-STARW1], Oregon State U, and the University of Texas-Austin [EPA-G2011-STAR-E1] International: ChemScreen (FP7, European Commission); Finnish Centre for Alternative Methods (FICAM); Center for Alternatives to Animal Testing (CAAT-US and CAAT-Europe) Industry: DOW Chemical Co; Stemina Biomarker and Discovery

Milestones

(Product 1) Virtual Embryo QA Plan (QA Category III) module for cell-agent based model (ABM) developed from empirical data and biological knowledge of angiogenesis	Scheduled: Q1 - 2012 Completed:
(Product 1) Publication and release of angiogenesis ABM including a proof-of-concept with thalidomide reference compounds and targeted assay data	Scheduled: Q2 - 2012 Completed:
(Product 1) Initial deployment of the angiogenesis ABM for toxicological assessment and linkage to developmental toxicity in predictive models for pregnant rats and rabbits	Scheduled: Q3 - 2012 Completed:
(Product 1) Forward validation of the vascular disruptor hypothesiswith a set of chemicals selected from the 21st century tools workplan	Scheduled: Q4 - 2012 Completed:
(Product 1) Assuming success in milestones 1-4, begin working with Program Offices moving the angiogenesis model to QA Category II	Scheduled: Q1 - 2013 Completed:
(Product 2) Virtual Embryo QA Plan (QA Category III) module for cell-agent based model (ABM) developed from biological knowledge of limb-bud morphogenesis	Scheduled: Q2 - 2012 Completed:
(Product 2) Version 1.0 release of Virtual Tissue Knowledgebase (VT-KB) tool for high-throughput text-mining and virtual embryo adoption centerframework for expert curation	Scheduled: Q3 - 2012 Completed:
(Product 2) Publication and release of limb-bud ABM including sensitivity analysis for signaling network (FGF, SHH, BMP) and proof-of-concept systems model with reference compounds (e.g., 5-fluorouracil) for predicting dysmorphogenesis	Scheduled: Q4 - 2012 Completed:
(Product 2) Beta-release of Morphogenesis Manager interface providing a user-friendly approach to parameterize de novo ABMs for in silico testing and sensitivity analysis	Scheduled: Q1 - 2013 Completed:
(Product 2) Conceptual model for male or female reproductive tract morphogenesis to address the developmental toxicity of male or female phenotypes in a cellular ABM	Scheduled: Q3 - 2013 Completed:
(Product 3) Acquire, evaluate and profile predicted redox-disruptor chemicalsin the ToxCast library using the mouse embryonic stem cell (mESC) adherent cell differentiation assay and novel biomarker proteins (eg, Gsc, Abcg2 transporter)	Scheduled: Q3 - 2012 Completed:
(Product 3) Delineate time course of normal angiogenesis in the zebrafish embryo (ZFE) vascular development screening tool utilizing phenotypic and proteomic endpoints	Scheduled: Q4 - 2012 Completed:
(Product 3) Forward validation of the redox disruptor hypothesisin the mESC platform with a set of ToxCast chemicals selected from the 21st century tools workplan	Scheduled: Q1 - 2013 Completed:
(Product 3) Corroborate the ZFE angiogenesis prototype using known angiogenic or anti-angiogenic reference compounds using cellular imaging protocols	Scheduled: Q2 - 2013 Completed:
(Product 3) Functional analysis of selective redox signaling pathway inhibitors in the mESC platform, serving to characterize genetic signals and responses for assay development	Scheduled: Q3 - 2014 Completed:
(Product 4) Establish cell culturing facility and cell lines to evaluate kinetic modulators	Scheduled:

(such as metabolism, transport, clearance rates, and tissue partition coefficients) to support kinetic modeling and blood:milk partitioning for trans-lactational neonatal exposure pathways (NERL)	Q4 - 2012 Completed:
(Product 4) Evaluate in vitro methodologies for investigating trans-placental fetal exposure to environmental chemicals (NERL)	Scheduled: Q2 - 2013 Completed:
(Product 4) Collection and integration of ADME data to develop life-stage models for estimating xenobiotic transfer pathways in the fetus and/or neonate (NERL)	Scheduled: Q2 - 2013 Completed:
(Product 4) Work with Program Offices, NTP/NIEHS, National Childrens Study, NCEA, DfE and NHANES to integrate biomonitoring data with developmental toxicity and exposure models (NERL will contribute to defining the exposure component of this milestone; linking NHANES data with exposure pathways such as trans-lactational)	Scheduled: Q4 - 2014 Completed:
(Product 4) Integration of exposure and PK/TK data for maternal-fetal/neonatal life-stage models into cellular ABMs developed in Products 1-2 (NERL will provide PK data for this milestone)	Scheduled: Q2 - 2014 Completed:
(Product 5) Virtual Embryo QA Plan (QA Category III) module for cell-agent based model (ABM) for neural crest and somite development	Scheduled: Q3 - 2012 Completed:
(Product 5) A cell ABM developed from empirical data and biological knowledge of neural crest migration and somite development (TIVS)	Scheduled: Q1 - 2013 Completed:
(Product 5) Evaluate effects of xenobiotics on multiple differentiation outcomes using qNPA for selected genes/pathways in the mESC platform	Scheduled: Q3 - 2013 Completed:
(Product 5) Test putative vascular disrupting chemicals identified in ToxCast with the ZFE vascular development screening tool using both imaging and proteomic endpoints	Scheduled: Q1 - 2014 Completed:
(Product 5) Test predictions from in silico models with relevant in vitro studies (ZFE, mESC, cultured organs) and targeted in vivo studies (e.g., Xenopus and pregnant rats)	Scheduled: Q3 - 2014 Completed:
(Product 6)Link modular virtual tissue models for angiogenesis and limb-bud morphogenesis into an integrated testing platform for developmental toxicity	Scheduled: Q4 - 2014 Completed:
(Product 6) Iterative collaboration between computational modelers and laboratory investigators to provide experimental data supporting the principles, concepts, and possible solutions of in silico virtual tissues for predictive toxicology	Scheduled: Q4 - 2015 Completed:
(Product 6) Develop computational model of mESC differentiation to characterize the critical decision points within sensitive pathways of differentiation	Scheduled: Q4 - 2016 Completed:
(Product 7) Models that integrate exposure with effects to aid life-stage specific exposure estimation and reconstruction, and chemical risk assessment (NERL)	Scheduled: Q4 - 2016 Completed:
(Product 7) Work with Program Offices to complete a fully integrated Virtual Embryo Quality Assurance Project Plan, including elements of QA Category III and Category II (NERL will provide the QA plan for the experimental data NERL collects such as ADME, PK, etc.)	Scheduled: Q4 - 2016 Completed:

Division Approved Yes

CSS

Data Collection and Computational Modeling for the "Virtual Liver"

CSS 221 221

Imran Shah
NCCT
IO

Topic/Theme

2 Systems

Project

2.2 Systems Modeling of Specific Tissues and Multi-Organ Pathways

Associated Project

None

Task Description

The Virtual Liver project will deliver an in silico framework to support decisions on the likelihood of hepatic effects for environmental chemicals with an emphasis on predicting mode of action (MOA) and human relevance The project leverages available quality controlled in vitro High Throughput Screening (HTS), -omic data and public domain sources of biomolecular information to develop, validate, and use computational tools for prediction of toxicity and prioritization for further testing. One of the key products of the Virtual Liver is a multi-scale systems modelling tool to quantitatively translate in vitro pathway perturbations of chemicals to their in vivo effects. The Virtual Liver products will be made available in Dashboards (CSS Topic 7) for assessing the hepatotoxicity of chemicals and mixtures. The Virtual Liver project aimed at addressing EPA regulatory needs and leverages collaborations with research groups in other US federal agencies, the European Commission (EC), academic/non-profit institutions, and some partnerships with commercial entities. We are developing a Level 3 Quality Assurance Project Plan (QAPP) to ensure that products of this research meet EPA standards and are scientifically defensible. The QAPP and associated standard operating procedures (SOPs) will describe our criteria for selecting data sets from HTS experiments, in-life studies, and the literature. This will also include techniques for building and parameterizing computational models, and for evaluating their predictions.

Rationale and Research Approach

The liver is a common target for chemicals and drugs due in part to the role of the liver in providing a first line of defense against xenobiotic-induced systemic damage. For ToxCast chemicals, many have some effect in the whole liver of mice or rats (including liver hypertrophy) and effects on cell morphology (for example, steatosis, necrosis, apoptosis, and cell proliferation). In 2-year bioassays, 30% or 9% of the ToxCast Phase I chemicals caused neoplasms in the mouse or rat liver, respectively. Importantly, the liver is often the most sensitive target in the 2-year bioassay irrespective of cancer induction. NOAELs/LOAELs have been established at least partially based on effects in the liver for 45% or 37% of ToxCast Phase I chemicals in mice or rats, respectively. Much is known about mechanisms of liver toxicity, but important data gaps remain that preclude accurate risk assessments for data-poor compounds. These include incomplete knowledge of the key events in individual modes of action (MOA) as well as human relevance of many MOA. The overarching goal of the Virtual Liver (v-Liver) project is to develop an integrated suite of computational models with which to elucidate hepatic pathways of toxicity and to simulate mechanistically-relevant dose-response relationships under different human exposure scenarios. A focus on the human liver is driven by the regulatory challenges in evaluating human hepatic effects, however, the approach may be extended to other species, provided there is a regulatory need to do so. Our approach complements standard and HTS-based hazard identification and will enable the rapid development of quantitative predictive models to analyze and understand incipient events underlying liver toxicity. This knowledge can then be used to select targeted confirmatory studies in a tiered toxicity testing paradigm for new environmental chemicals for which data gaps exist. This integrated strategy will use data from diverse experimental methods, including in vitro molecular assays/profiling data including epigenetics, gene, microRNA,

protein and metabolite changes as well as quantitative histomorphometry of cell fate to develop computational tools including: physiologically based toxicokinetic (PBTK) to estimate absorption, distribution, metabolism and excretion (ADME) of chemicals; knowledge-bases to analyze pathways to hepatotoxicity; and Virtual Tissues to simulate the dose and time dependent changes in these pathways. Predicting chemical-induced hepatotoxicity is an open problem that presents many scientific challenges. Hence our strategy is based on incrementally analyzing and modeling the dosimetry and the effects of chemicals on hepatic adverse outcome pathways (AOPs). AOPs describe the linkages between early molecular initiating events, downstream cellular phenotypes and long-term histopathological outcomes related to hepatic dysfunction. Our research aims to map events preceding apical endpoints and so that we can estimate the incipient effects of chemicals before frank toxicity is observed. An incremental systems approach for modeling AOPs will help identify sources of uncertainty that could improve performance/confidence of our predictive tools. We will test the hypothesis that 1) environmental chemicals can activate one or more signaling pathways, stimulating intracellular processes that alter cell phenotypes (for example, but not limited to, steatosis, proliferation, necrosis, apoptosis), potentially leading to adverse liver effects (such as steatohepatitis, fibrosis, proliferative lesions) and 2) mechanistic, multi-scale computational modelling can capture this process, allowing quantitative prediction of certain types of liver injury by translating in vitro data on absorption, distribution, metabolism and excretion (ADME), molecular and cellular events to in vivo histopathological lesions. Although histopathological alterations do not always result in a permanent impact on health, we consider them an important predictive goal because they are the clinical standard for diagnosing disease state. Delivering this framework will require the integration of computational and experimental tools and expertise in hepatotoxicology and systems modeling in a manner that incrementally advances the portfolio of current risk assessment techniques. The specific aims of this research are to work collaboratively with risk assessors (and stakeholders from within the EPA, other US federal agencies, European Commission (EC), international organizations, academic/non-profit institutions, and commercial entities) to identify and transparently implement the best practices for: (a) efficiently screening chemicals for hepatic effects; (b) elucidating pathways driving these adverse effects, which may also guide targeted in vitro and in vivo confirmatory tests; (c) estimating chemical-specific parameters involved in their ADME; and (d) integrating dosimetry and pathway perturbations in a holistic framework to estimate hepatic effects under different exposure scenarios. To ensure relevance to EPA needs, the Virtual Liver will focus on case studies from EDSP21, TSCA21, OPP21 and OW21, in addition to reference hepatotoxicants and compounds from the broader ToxCast program with bioactivity signatures predictive of hepatotoxicity. By determining the chemical-specific factors that relate multiple routes of exposure (including inhalation, ingestion, and contact/dermal) to liver-specific dosimetry, we will both link to specific exposure scenarios (where available) and, lacking exposure data, make reverse toxicokinetic predictions of equivalent exposures sufficient for adverse hepatic outcomes. Our long-term goals are to incrementally enhance v-Liver by gathering additional experimental data to quantitatively investigate the impact of genetic polymorphisms, gender, life-stages, disease state and other susceptibilities on ADME, and on events in AOPs. Understanding the impact of fetal exposures on later life effects in the liver is a goal shared with CSS 2.2.2. PRODUCTS (a) Screening Hepatic Effects. Chemicals, prioritized with respect to predicted hepatic dosimetry, will be screened for a wide range of acute, subchronic, and chronic adverse in vivo effects, including outcomes related to cancer (e.g., cell fate changes) and non-cancer processes (e.g., steatohepatitis, hepatic lipidosis). These liver toxicity end-points will be used to statistically anchor -omic and HTS data to produce signatures that empirically map short-term molecular events with adverse effects. These signatures will be useful for rapidly screening large sets of environmental chemicals for potential hazard. In addition, the accuracy of these signatures (for identifying reference hepatotoxicants) provides an important baseline for evaluating the performance / justification for more complex models. (b) Pathways to Hepatotoxicity (AOP). One of the key challenges of this research is to relate the in vivo progression of acute, subchronic and chronic hepatic histopathological effects (such as fibrosis, neoplastic lesions, etc.) to incipient molecular and cellular events, which can be observed in vitro. We will work with Program Office and Regional partners to select the adverse hepatic outcomes where there are unmet regulatory needs. It is vital to identify early surrogates of in vivo toxicity that can be assessed in vitro, as there are few established predictive markers of hepatotoxic effects. This activity will focus on reference hepatotoxicants to produce a knowledge-base (KB) to organize evidence on hepatic functions using ontologies, literature, and signatures associated with these functions. In

addition, a tool will be produced to elucidate the putative pathways to adverse hepatic effects, which can be used by domain experts to guide targeted confirmatory molecular and cellular tests. (c) Linking Exposure to Tissue Dosimetry. In order to estimate dose-dependent effects, v-Liver bridges (oral, dermal and inhalation) exposure with cell-level concentration by modeling ADME using PBTK and microdosimetry modeling for the hepatic lobule. The chemical-specific parameters for absorption, distribution and (hepatic) metabolism are being collected using in-house studies (NERL/NHEERL), external collaborations (The Hamner Institute) and contract research. Parameters that cannot be measured are currently estimated using published quantitative structure activity relationships (QSARs) models. Clearance is a complex process which requires an understanding of active and passive transport of a foreign chemical and metabolites across biological membranes. The net outcome for cellular concentration thus depends on the interplay between transport proteins (influx and efflux) and xenobiotic metabolizing enzymes. For each chemical a PBTK model with multiple routes of exposure is parameterized using a combination of in vitro measurements and published QSAR models. The model will be developed and refined incrementally using in vitro assays for metabolic clearance, rates of absorption via different routes, Phase I and II metabolism, and active transport (in some cases). Confidence in liver dosimetry predictions will be evaluated with respect to uncertainty in data used, known variability in relevant physiology, and compared to available human and/or rodent toxicokinetic data. (d) Computer simulation of dose-dependent hepatic effects. The Virtual Liver (v-Liver) will be used to simulate in vivo context for AOPs (of regulatory importance) at environmentally relevant exposures. Whereas in vitro models allow assessment of chemical-induced molecular and cellular changes, linking these perturbations to in vivo effects across chemicals, dose, time and species remains challenging. In vivo, cells exist within the context of a tissue with differentiated cell types, inherent spatial and temporal gradients, and inter-cellular signaling. As a cellular systems model of hepatic lobule (and ultimately liver function), v-Liver acts as a crucible for in vitro data, modeling assumptions, and literature-derived relationships comprising a knowledgebase of hepatic biology and toxicity. Modeling a normal, functional liver ensures recapitulation of known biology and identifies knowledge gaps. As such, v-Liver provides a framework for integrating multiple, potentially conflicting, sources of data in order to predict the impact of chemical perturbations that have been characterized in vitro. The tools and approaches are highly modular to facilitate evaluation of multiple liver-relevant AOPs. The v-Liver microdosimetry approach enables quantitative linkage between liver effects and pharmacokinetics, i.e. circulating xenobiotics and their metabolites as well as endogenous molecules. This project will investigate uncertainty in the predictions as well as variability due to causes including alternative physiologic pathways.

Outputs from Projects related to this task

Linkage of gene expression/pathways with phenotypic outcomes in the intact rodent liver.

Expected Products

(1) Computational model of the hepatic lobule that accounts for extrapolation from in vitro hepatoxicity data to in vivo. The product will utilize ToxCast data and knowledge-based tools to construct dynamic molecular networks, estimate cell level concentrations based on microvascular transport, and predict chronic hepatic effects on selected EDSP21/TSCA21/OW21 chemicals (chemicals selected in collaboration with OSCPP).

Type: DATA
MODEL

Delivery Date (FY): 2012

(2) Data to assess the mechanisms and kinetics of xenobiotic transformations, transport, enzyme induction, enzyme inhibition, and pathway elucidation. This product will support development of computational (in silico) models linking exposure-to-effects via internal dose for characterizing and mitigating the effect of ADME on HTS liver assay results used in chemical prioritization and risk assessment. The product will initially focus on selected chemicals relevant to EDSP21 and TSCA21 Dashboards and will provide empirical data for models to predict the influence of transporters on hepatic clearance and microdosimetry.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(3) Data generation and functional analysis of AOP descriptions for phenotypic assessment of altered gene function. This product will provide HCS data to experimentally anchor specific toxicity pathways to hepatocyte function effects that can be integrated into predictive virtual tissue models of carcinogenesis and hepatotoxicity.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

4) Quantitative dose response models predicted by biological networks governing hepatocyte death and proliferation underlying 20 ToxCast chemicals with activity on nuclear receptor pathways. This product will develop a cell agent-based model for estimating acute and chronic effects of hepatic AOPs and a computational framework to integrate these effects with environmental processes (activity patterns, PBPK/microdosimetry, mechanistic models) for selected chemicals in EDSP21/TSCA21/OW21/OPP21.

Type: DATA
MODEL

Delivery Date (FY): 2013

(5) Expansion and integration of the virtual liver toolbox. This product will plug-in other key pathways to the toolbox, including adipogenesis and regional oxygen gradients. Information from in silico models will be corroborated by in vitro work (hepatocytes, complex cultures, small model organisms) and targeted in vivo studies. Product development will be guided by cell-agent based models and cell-imaging data, and implemented for 10 chemicals in EDSP21/TSCA21 with relevant activities in ToxCast.

Type: DATA
SOFTWARE

Delivery Date (FY): 2014

(6) Expansion of an integrated Virtual Liver model into an integrated testing platform for predictive hepatotoxicity . The integrated Virtual Liver model will expand from iterative collaboration between computational modelers and laboratory investigators to incorporate additional data and parameters supporting the principles, concepts, and possible solutions of in silico virtual tissues for predictive toxicology (e.g., combining models for microdosimetry, angiogenesis, hepatic carcinogenesis).

Type: DATA
MODEL

Delivery Date (FY): 2016

(7) Models that support the integration of exposure with effects through metabolic transformation, chemical-chemical interactions, and resulting changes in toxicity of a chemical stressor in hepatic and intestinal systems (e.g., QSAR and ADME models for conazole clearance and transport).

Type: DATA
MODEL

Delivery Date (FY): 2016

Start Date Q1 2012

End Date Q4 2016

Cross Research Project Output Supported?
Maybe

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)
NCCT: Wambaugh, Setzer, Jack NHEERL: J

External Collaborators (known or proposed)
TBD

Simmons, Kenyon, Hughes, McDonald, Sey, Thai, Blackman, Jones, Ross, Winkfield, Wood, Moore, Chorley, Nelson, Hester, Corton, S Simmons, El-Masri, Carswell, Evans, McQueen NERL: Kenneke, Mazur, Marchitti

Milestones

(Product 1) Mechanistic cross-talk model of hepatocyte proliferation, necrosis, apoptosis & microdosimetry estimates for ToxCast chemicals. Deliver model using prototype (VT-KB) widget for v-Liver Workbench	Scheduled: Q1 - 2012 Completed:
(Product 1) Linkage of ToxCast assays into hepatocyte model & quantitative evaluation using chemicals	Scheduled: Q2 - 2012 Completed:
(Product 1) Integration of microdosimetry and hepatocyte model into virtual lobule to relate oral exposure to tissue effects. Deliver prototype for v-Liver Workbench.	Scheduled: Q3 - 2012 Completed:
(Product 2) PK data on partitioning for select ToxCast chemicals to estimate distribution (NERL)	Scheduled: Q2 - 2012 Completed:
(Product 2) Data on biotransformation for select ToxCast chemicals to estimate metabolism (NERL)	Scheduled: Q3 - 2012 Completed:
(Product 2) Data on hepatic transporters for select ToxCast chemicals to improve dosimetry estimates(NERL)	Scheduled: Q4 - 2012 Completed:
(Product 2) Gathering and Combining experimental (in vitro and in vivo) data with QSAR models to fill in data gaps for PBPK model developments for selected chemicals (in collaboration with extrapolation)(NERL will provide experimental ADME and PK data and contribute QSAR models)	Scheduled: Q1 - 2013 Completed:
(Product 2) Development and evaluation of PBPK models for selected chemicals to link liver dosimetry with exposure models (In collaboration with extrapolation)(NERL will provide experimental ADME and PK data)	Scheduled: Q3 - 2013 Completed:
(Product 2) Fill data gaps in ADME of select ToxCast chemicals to improve dosimetry estimates (NERL will provide experimental ADME and PK data)	Scheduled: Q4 - 2013 Completed:
(Product 3) Identification of adverse hepatic effects/cancer from analysis of AOPs. Deliver prototype VT-KB graphical interface (for v-Liver Workbench) to organize literature and ToxRefDB evidence.	Scheduled: Q1 - 2012 Completed:
(Product 3) Empirically derive signatures for hepatic effects/cancer by phenotypic anchoring with ToxCast and published -omic data. Deliver prototype widget to use signatures in prioritization for v-Liver Workbench	Scheduled: Q2 - 2012 Completed:
(Product 3) Organize evidence for putative hepatotoxicity/cancer pathways from literature, ToxRefDB, ToxCast into VT-KB. Deliver VT-KB curation, search and visualization interface for v-Liver Workbench	Scheduled: Q3 - 2012 Completed:
(Product 3) Evaluate and refine putative hepatotoxicity/cancer pathways for reference and environmental chemicals using -omic histomorphometric data	Scheduled: Q4 - 2012 Completed:
(Product 3) QA documents and in vivo dosing protocols approved in preparation for in vivo experiments to support the development of a predictive model of hepatotoxicity	Scheduled: Q4 - 2012

FY13-1 Generate data on putative "key" events in hepatotoxicity/cancer pathways for reference and environmental chemicals using HCS (quantitative for dose-response estimation)	Completed:
(Product 3) Refine putative hepatotoxicity/cancer pathways based on new evidence in VT-KB.	Scheduled: Q2 - 2013 Completed:
(Product 4) Utilizing existing data on critical pathways for carcinogenicity (e.g ERK1/2, nuclear receptors) for selected chemicals (e.g. conazoles) to develop mechanistic computational models illustrating data needs and utility of such models	Scheduled: Q2 - 2012 Completed:
(Product 4) Mechanistic models of cellular phenotypes based on putative hepatotoxicity pathways (e.g. Immune cell activation, stellate cell activation) . Deliver model in v-Liver Workbench	Scheduled: Q1 - 2013 Completed:
(Product 4) Evaluation of cell-based models using ToxCast and HCS data / Improved of microdosimetry estimates using new ADME data for environmental & reference chemicals	Scheduled: Q2 - 2013 Completed:
(Product 4) Integrate cell-based models and microdosimetry in virtual tissues to predict quantitative dose-response for environmental chemicals.	Scheduled: Q3 - 2013 Completed:
(Product 5) Use VT-KB to elucidate putative toxicity pathways for EDSP21/ TSCA21 chemicals	Scheduled: Q4 - 2013 Completed:
(Product 5) High-throughput estimation of ADME parameters for EDSP21/ TSCA21 chemicals	Scheduled: Q1 - 2014 Completed:
(Product 5) Targeted testing of EDSP21/ TSCA21 chemicals using in vitro studies using putative toxicity pathways	Scheduled: Q2 - 2014 Completed:
(Product 5) Virtual tissue simulation estimates of human oral equivalents for hepatic effects for EDSP21/ TSCA21 chemicals/mixtures using in vitro and ADME data	Scheduled: Q3 - 2014 Completed:
(Product 6) Similar Milestones to Product 5	Scheduled: Q3 - 2014 Completed:
(Product 7) Linkage of PBPK models with empirical information from AOPs and signature hepatic effects for to develop PBTK/PD models (in collaboration with extrapolation)(NERL will provide experimental ADME and PK data)	Scheduled: Q2 - 2013 Completed:
(Product 7) Linkage of exposure models with PBPD models to describe dose-response relationships. Evaluation of the exposure-dose response models with their applicability in risk (In collaboration with evaluation)(NERL will provide experimental ADME and PK data)	Scheduled: Q4 - 2013 Completed:

Division Approved Yes

CSS Systems models linking reproductive and neurodevelopmental effects to endocrine disruption

CSS 223 223 **Joe Tietge**
NHEERL
MED

Topic/Theme

2 Systems

Project

2.2 Systems Modeling of Specific Tissues and Multi-Organ Pathways

Associated Project

None

Task Description

This task is focused on the development and application of endocrine models as tools that can be used in a variety of regulatory contexts, including: (1) virtual screening of individual chemicals and chemical classes; (2) enabling quantitative predictions of hazard, (3) establishing the biological basis for rapid test development; (4) providing the necessary pathway knowledge to improve interpretation of in vitro assay results; (5) supporting decisions regarding the use of targeting testing; and (6) establishing the biological basis for cross-species extrapolation. Although our understanding of the complex biology of the endocrine pathways has grown significantly over the past decade, as has our understanding of how xenobiotics affect endocrine homeostasis, significant work remains to be done to support the development of quantitative endocrine models suitable for use in decision-making. This task will develop and use pathway-based information to establish transitional linkages among various levels of biological organization. These linkages will provide the rationale and scientific foundation to utilize sub-organismal data in regulatory decisions, thereby reducing the need for whole organism toxicity studies. Thus, this work encompasses a diversity of approaches, conducted in parallel, to provide the necessary information for endocrine model development, to discover and define novel toxicity pathways, and to establish linkages among key events in relevant adverse outcome pathways (AOPs).

Rationale and Research Approach

Endocrine pathways in vertebrates are known to be critical to the control of growth, development, and reproduction, The hypothalamic-pituitary-gonadal (HPG) and the hypothalamic-pituitary-thyroid (HPT) axes are of particular interest, as there is clear evidence that environmental chemicals can disrupt normal regulation and activity of these pathways. Furthermore, the HPG and HPT axes have been identified as high priority pathways by the Administrator and thus, are the principle hormonal pathways being regulated under the Agencys Endocrine Disrupter Screening Program. Disruption of these pathways can lead to adverse outcomes relevant to regulatory concerns in both human health and ecological risk contexts, such as neurodevelopmental deficits and reproductive impairment. Although the initial focus of this task is on the HPG and HPT pathways, it is well recognized that regulation of other endocrine pathways, such as the hypothalamic-pituitary-adrenal axis, may be interrelated. Therefore, this work may require knowledge of the interaction among endocrine pathways to provide sufficient information to develop valid, predictive models. . At this time no new research is planned for the hypothalamic-pituitary-adrenal axis. The major objective of this Task is to develop virtual endocrine models of the HPG and HPT axes that provide the Agency with enhanced methods to interpret data and quantitatively predict effects on these pathways, including the consequences of disruption. These models will be built with empirical results and computational approaches that incorporate relevant information on molecular targets and the cellular, tissue, and organismal outcomes that occur in responseto chemical exposure. Since endocrine pathways are particularly important during development, this work will take into account sensitive lifestages and the specific exposure domains associated with those lifestages. Inherent in the development of these models is the need to incorporate the complex compensatory feedback mechanisms that exist in the endocrine axes and

enable resilient system behavior. This challenging task is further complicated by the multiple mechanisms by which these systems can be perturbed by environmental chemicals. Conceptual and computational endocrine models will be developed iteratively, building upon the broad, existing scientific knowledgebase. Fundamental information regarding these pathways will be gathered through conventional and advanced data mining efforts and this information will be evaluated to identify data gaps concerning key model linkages. Empirical testing with chemicals known to perturb specific activities will be used both to generate data to further populate and parameterize the model constructs. Additional studies will be conducted to validate model predictions against real experimental data, and to assess model performance for continued improvement/refinement. In order for this work to be realistic, however, it is important that the scope extend beyond the relatively narrow, classical definitions of hypothalamic-pituitary-endocrine (HPx) axes. For example, homeostatic control and activity of hormones is achieved by a combination of HPx activity (e.g., classical negative feedback mechanisms) and the activities of various processes outside of the HPx, such as hepatic metabolism. Furthermore, the different hormonal pathways do not function in isolation of other pathways. Consequently, the role of the non-HPx activities and the interaction among different pathways warrants consideration when modeling the behavior of a particular endocrine pathway of interest. Thus, the core approach of this research is to identify and characterize toxicity pathways that both reflect and predict normal and abnormal function, taking into consideration the impact of the broader physiological and neurodevelopmental environment. This information will then be used to construct computational models of the HPG and HPT pathways capable of simulating behavior and predicting outcomes in response to chemical exposure. A major outcome of this approach will be to define a key biological events for use in sub-organismal endpoints measured in in vitro and in vivo studies. This includes efficient, high-throughput and medium-throughput screening (HTS/MTS) assays to evaluate chemicals for effects on the endocrine axes. These assays will be selected and/or developed to identify effects on specific cellular processes and serve as an aid for chemical prioritization and informing targeted-testing. They will be designed and adapted for testing individual chemicals, chemical libraries of interest, and environmental samples, as appropriate. These assays will provide the data needed to better define the inherent chemical properties responsible for endocrine disrupting properties and provide key effects information for structure-activity analyses within the various endocrine axes. This work will provide the needed quantitative and qualitative tools to translate in vitro data into predictions of outcomes at the level of the organism by adding biological context to the in vitro observations. This is critically important as HTS/MTS methods proliferate, because the value of the voluminous information is dependent upon a scientifically sound and rigorous interpretation that depends upon rational model constructs. Ultimately, the long term vision for this work is to develop sufficiently comprehensive endocrine pathway models that are able to provide quantitative estimates of risk, with an emphasis on developmental and reproductive outcomes. These estimates will be based on validated linkages among different levels of biological organization that enable a transition away from whole organism toxicity testing.

Outputs from Projects related to this task

1. This research will develop computer programs to predict the effects of chemicals on hormones in the body. These programs will specifically provide in silico, quantitative model(s)of HPG and HPT pathways to predict endocrine toxicity. 2. This research will develop ways to use information from cells and tissues to tell us how chemicals can change hormones in the body. This will be used to help scientists and managers decide if some chemicals need to be controlled using environmental laws. The methods will include quantitative and qualitative analytical approaches to interpret the implications of HTS/MTS/in vitro data regarding endocrine pathways to outcomes at the organismal level in support of regulatory decision making.

Expected Products

(3) Development of a computational (in silico) systems model that simulates key aspects of a chemicals potential to disrupt normal HPG axis regulation, linking changes in key events within adverse outcome pathways (chemicals selected from EDSP21).

Type: DATA
MODEL

Delivery Date (FY): 2013

(4) PATHFINDER: Proof-of-concept that the transgenic Xenopus tadpole is a useful bioindicator of a thyroid endocrine signal. This product will determine its effectiveness in detecting the presence of EDCs that impact the thyroid axis, including a limited validation via testing of positive controls, known mammalian responses, and identification of a suite of thyroid-responsive genes for screening purposes.

Type: OTHER

Delivery Date (FY): 2013

(5) Implementation of a computational systems model capable of simulating key aspects of the feedback/compensatory response and of identifying a chemicals potential to disrupt normal regulation of the HPG axis for EDSP21. This product will serve as a screen for chemicals with the potential to disrupt normal function of the gonadal and adrenal axes for human health, and as a point of comparison with similar studies in wildlife species that could be used for extrapolation purpose.

Type: DATA
MODEL

Delivery Date (FY): 2015

(6) Develop a computational systems model of the thyroid axis that will facilitate extrapolation from chemical exposure to effects, based upon mechanistic endpoints. This product will advance understanding of the critical pathways for complex interplay of chemical exposure, molecular targets, circulating thyroid hormones, and adverse effects.

Type: DATA
MODEL

Delivery Date (FY): 2016

(7) Extramural research (STAR grants) to develop high-throughput assays for predictive modeling of reproductive and developmental toxicity modulated through the endocrine system or pertinent pathways in humans and species relevant to ecological risk assessment.

Type: EXTRAMURAL DOCUMENT
GRANT

Delivery Date (FY): 2016

(1) Improve AOP models by incorporating key events data for the hypothalamic-pituitary-gonadal (HPG) axis. This product will inform the development of rapid test methods to define novel toxicity pathways in disruption of reproductive functions on selected chemicals from the EDSP21 case study (e.g., adrenal progesterone, neuropeptide regulation, steroid hormone metabolism)

Type: DATA
MODEL

Delivery Date (FY): 2013

(2) Systems models that link reproductive and developmental effects to thyroid disruption. These models will improve extrapolation between species and characterize uncertainties in the relationship between the key events and adverse outcomes; and these models will inform targeted testing for neurodevelopmental AOPs for chemicals selected from EDSP21/OPP21 case studies.

Type: DATA
MODEL

Delivery Date (FY): 2014

Start Date Q1 2012

End Date Q4 2016

Cross Research Project Output Supported?
Maybe

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)

NCCT: Richard Judson, Matt Martin, Thomas Knudsen NHEERL/TAD: Ralph Cooper, Mary Gilbert, Jerome Goldman, Gary Klinefelter, Mihael Narotsky, Tammy Stoker, Ashley Murr, Deborah Best, Daniel Hallinger, Juan Suarez, Lillian Strader NHEERL/ISTD: Kevin Crofton, Joan Hedge NHEERL/MED: Sigmund Degitz, Michael Hornung, Joseph Tietge, Joseph Korte, Patricia Kosian, Jonathan Haselman, Brian Butterworth

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Complete comprehensive assessment of available HTS/MTS/in vitro methods for endpoints relevant to HPG pathway	Scheduled: Q2 - 2012 Completed:
(Product 1) Conduct studies to improve understanding of the biology of the HPG pathway and identify critical processes and windows of developmental sensitivity.	Scheduled: Q4 - 2013 Completed:
(Product 1) Develop and use selected in vitro/in vivo methods to fill data gaps on critical processes in HPG pathway	Scheduled: Q4 - 2013 Completed:
(Product 1) Evaluate the effects of selected chemicals on HPG pathway responses using targeted, hypothesis-driven testing.	Scheduled: Q4 - 2013 Completed:
(Product 1) Discover, describe, and evaluate the interaction among different endocrine pathways using hypothesis-driven testing.	Scheduled: Q4 - 2013 Completed:
(Product 2) Complete comprehensive assessment of available HTS/MTS/in vitro methods for endpoints relevant to HPT pathway.	Scheduled: Q4 - 2012 Completed:
(Product 2) Conduct studies to improve understanding of the biology of the HPT pathway and identify critical processes and windows of developmental sensitivity.	Scheduled: Q4 - 2014 Completed:
(Product 2) Develop and use selected in vitro/in vivo methods to fill data gaps on critical processes in HPT pathway.	Scheduled: Q4 - 2014 Completed:
(Product 2) Assess comparative endocrine toxicity across taxa using selected chemicals representing specific molecular initiating events and/or MOA associated with HPT pathway.	Scheduled: Q4 - 2014 Completed:
(Product 2) Support the interpretation of in vitro assays that represent critical HPT pathway activities.	Scheduled: Q4 - 2014 Completed:
(Product 3) Delivery of version 1 of the Pathway Knowledgebase (PKB). This will include a compilation of public pathway databases, biomedical ontologies and chemical-assay data from EPA and external studies.	Scheduled: Q3 - 2012 Completed:
(Product 3) Delivery of version 1 of the multi-scale HPG pathway model based on PKB and in vitro assay results. This will allow for tracing of networks connecting molecular initiating events to molecular, cell, tissue and organ-level effects. This effort will result in candidate targets for assay development.	Scheduled: Q4 - 2012 Completed:

(Product 3) Perform targeted experiments on multiple human cell types, using steroid detection and genomics readouts to help refine the neuroendocrineendocrine pathway models with an initial focus on ER signaling.	Scheduled: Q2 - 2013 Completed:
(Product 3) Develop framework for building simulations on top of the pathway model.	Scheduled: Q4 - 2013 Completed:
(Product 4) Complete proof-of-concept testing of the TR²-GFP transgenic Xenopus model as a potential in vivo screen for thyroid active chemicals.	Scheduled: Q4 - 2012 Completed:
(Product 5) Extend the PKB to include experimental data (HTS, MTS, genomics, etc.) data created under earlier milestones.	Scheduled: Q4 - 2014 Completed:
(Product 5) Implement simulation capabilities to model behavior of single-cell in vitro experiments for treatment of selected compounds.	Scheduled: Q4 - 2014 Completed:
(Product 5) Perform targeted experiments to test and refine the models, including comparison of multiple cell types across the HPG axis.	Scheduled: Q4 - 2015 Completed:
(Product 6) Complete first-generation HPT computational systems model.	Scheduled: Q3 - 2012 Completed:
(Product 6) Extend the PKB to include experimental data (HTS, MTS, genomics, etc.) data created under earlier milestones.	Scheduled: Q3 - 2013 Completed:
(Product 6) Implement simulation capabilities to model behavior of single-cell in vitro experiments for treatment of selected compounds.	Scheduled: Q4 - 2013 Completed:
(Product 6) Perform targeted experiments to test and refine the models, including comparison of multiple cell types across the HPT axis.	Scheduled: Q4 - 2014 Completed:
(Product 7) Evaluate potential interactions with successful proposals and establish collaborative relationships, as appropriate.	Scheduled: Q4 - 2016 Completed:
(Product 1) Support the interpretation of in vitro assays that represent critical HPG pathway activities.	Scheduled: Q4 - 2013 Completed:

Division Approved Yes

CSS

Develop, Refine and Link Exposure to Dose Models

CSS 232 232

Haluk Ozkaynak
NERL
IO

Topic/Theme

2 Systems

Project

2.3 Metrics and Models that Define Chemical Exposures and Internal Dose

Associated Project

None

Task Description

Understanding and quantifying exposure is a critical element for character real-world risks for both humans and wildlife. The overall goal of this task is to obtain and incorporate the scientific knowledge on exposure and dose-related factors and data into exposure and dose-modeling tools that will allow integration with biologically-based systems models used for predicting health/environmental risks from chemical exposures. The new or refined models will include the capability for user-defined spatial and temporal resolution, including key landscape attributes. Exposure modeling will be conducted iteratively with biological modeling to identify and prioritize individual and population-level exposure factors, as well as develop required technologies to better predict the real-world exposures that will induce relevant perturbations. Research will be conducted to support the development and evaluation of newer, less data/input or computationally demanding, high-throughput, and transparent/readily accessible models. Application of linked exposure and dose models through case studies will support ORD research and Program/Regional Office needs.

Rationale and Research Approach

EPA needs a suite of targeted environmental exposure and dose models that can be used to characterize spatial/temporal variations in chemical concentrations in real-world environments to identify sources and pathways of exposure and to estimate both environmental exposure and the internal dose received by humans, plants and wildlife populations of concern. The need for screening and prioritization of thousands of chemicals based on predicted exposures (i.e., population, individual, organ or tissue level) as well as potential toxicity is also of great importance to EPA. The expected outcome from this task is enhanced exposure and dose estimation tools that would lead to reduced uncertainty in Agencys risk assessments and risk management decisions. In order to achieve this goal, the evaluated models will be integrated with the other tools within the source-to-outcome systems modeling area. The task outputs and products will inform CSS Task 2.4 on ecological assessments; link to physiologically based pharmacokinetic (PBPK) models developed under the CSS Task 4.1.1 on cumulative risk topic area, as well as share pertinent information with other ORD ITRs (e.g., incorporate childrens exposure factors data being developed under SHCRP). The research approach is aimed to enhance existing environmental exposure and dose models through five main activities: (1) environmental systems modeling approaches including enhanced fate/transport models with spatially or temporally resolved inputs/algorithms and a fully functional Environmental Fate Simulator (EFS); (2) SHEDS-Multimedia human exposure and dose model enhancements, evaluation, and program-specific applications; (3) developing a new more flexible and broadly applicable human exposure and dose model (SHEDS-Lite) for source-to-effects analysis applications for priority chemicals; (4) PK & PBPK models and toolboxes to support life-stage specific risk assessment modeling; and (5) application of linked human exposure and dose models through case studies to support ORD research, and Program/Regional Office needs. In these applications, SHEDS or SHEDS-Lite will be linked with PBPK models using input information derived from Task 2.3.1 and other related CSS, SHC research activities or available ORD/EPA sources. The EFS will represent the integration of the most robust process science available with state-of-the-art chemoinformatic tools for the

categorization of process science relating to chemical structure and chemical processes, and the modeling software technologies developed through ORDs Integrated Environmental Modeling (IEM) Program. These modeling technologies will allow for the seamless access to databases, and for parameterization and support of Agency environmental fate and transport models (e.g., IEMS, EFAST, PRZM/EXAMS, ChemSTEER, WPEM, IAQX). The SHEDS-Multimedia activity(well recognized and utilized by OPP in their various regulatory evaluations) will initially focus on refinements for the source-to-concentration module; longitudinal diary construction; dietary and residential merging algorithms; CHAD/METS research; uncertainty quantification; local-scale modeling (e.g., methyl mercury via fish consumption). Case study applications will involve developing population distributions of exposure (variability & uncertainty); identifying key pathways, factors, and data needs; linking to PBPK models; and evaluating model predictions against measurements. SHEDS-Lite model will predict human exposures and also internal dose when linked with appropriate PBPK models. SHEDS_Lite is being developed specially to address Program Office requests for models that do not require extensive and expensive sets of data. SHEDS-Lite will also be designed to support ORD/NCCTs ExpoCast, ToxCast, and Expo (Pi) systems through the generation of suitable metrics to screen or evaluate chemicals based on biologically and physically relevant human exposures. Furthermore, this model will also facilitate evaluation of concentrations used in high-throughput assays/ToxCast studies in terms of determining environmentally relevant exposures. Development of this new model will begin by using the higher-tier SHEDS-Multimedia Model in formulating a more efficient and universal modeling methodology for priority CSS chemicals. However, SHEDS-Lite will include a number of code simplification schemes such as reducing the number of inputs, simulations and the number of diaries and events required; modifying daily simulation time steps; emphasizing key exposure pathways; increasing numerical efficiency of the code; and employing a non-SAS based platform. A number of approaches will be taken to enhance the development of PBPK models. To better address population variability and uncertainty, in addition to informing exposure routes and species to species extrapolations, parameter databases and estimation tools will be developed and incorporated into the recently produced PReParE (Physiologically Relevant Parameter Estimation), an in silico intranet-accessible framework. These products will support PBPK and dosimetry model development and their applications within the Agency, as well as exposure-dose extrapolation research. This PBPK toolbox will include a variety of QSAR based estimates of dermal absorption, multi-species tissue expression profiles, intelligent literature parsing scripts of key information (e.g., natural language processing) and libraries of molecular targets related to population (SNPs) variability and life-stage sensitivity (i.e., ontogenic library of critical proteins). This work integrates directly with Research Task 1.3.2 under the Inherency Research Theme since similar, yet discrete initiatives, are embodied within PReParE. Finally, application of coupled models developed and refined under this task will support Program Offices (e.g., OCSPP, OCHP, and OW) and Regional Offices for priority case studies, including focus on vulnerable life-stages (e.g., children) and populations (e.g., communities at disproportionate risk; cross-walk with SHCRP).

Outputs from Projects related to this task

(1) algorithmsNew & refined stand-alone & integrated spatially &temporarily resolved environmental models and simulators (e.g., IEMS, EFAST, PRZM/EXAMS, WPEM, IAQX) (2) Refined SHEDS & new SHEDS-Lite models (3) PK & PBPK models and toolboxes (4) Applications of linked models to address Program Office and Regional priorities

Expected Products

(12) Updated version of PReParE (Physiologically Relevant Parameter Estimation) to include tissue specific expression profiles of multiple species and humans.

Type: DATA
MODEL

Delivery Date (FY): 2014

(5) Documented SHEDS- fugacity model that will predict multimedia indoor concentrations based on chemical properties and scenarios, Publication(s) of SHEDS (and linked with PBPK models) applied to support higher tier assessments

Type: DATA

Delivery Date (FY): 2013

MODEL

(3) Fully Functional Environmental Fate Simulator that will provide estimated environmental concentrations of chemicals in a spatially explicit manner.

Type: DATA
SOFTWARE

Delivery Date (FY): 2014

(6) Application of SHEDS modeling that provide support to Regions and community-scale case studies (cross-walk with SHC).

Type: DATA
MODEL

Delivery Date (FY): 2014

(10) Public/web release of SHEDS-Lite methodology and its applications to prototypical CSS chemicals.

Type: OTHER

Delivery Date (FY): 2016

(1)Environmental Systems Model: Through linkage to web-accessible databases will provide the necessary environmental descriptors necessary for the parameterization of environmental fate and transport models.

Type: DATA
MODEL

Delivery Date (FY): 2012

(2) Reaction Pathway Simulator (Version 2.0) that provides the dominant transformation pathways and products of chemicals for reductive transformation, hydrolysis, photolysis, water disinfectant mediated oxidations and aerobic/anaerobic biodegradation as a function of environmental conditions.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(4) Revised version of SHEDS-Multimedia (v4) as recommended by 2010 FIFRA SAP to included output results for different scenarios, case-studies and sensitivity analyses addressing OPP needs including dietary and residential scenarios

Type: DATA
SOFTWARE

Delivery Date (FY): 2012

(7)Evaluation and contribution to further development of lower tier assessments using SHEDS model output results, including sensitivity analyses ; SHEDS model output results for different scenarios and analyses for higher tier assessments of priority to Program Offices;

Type: OTHER

Delivery Date (FY): 2014

(8) Prototype SHEDS-Lite model including linkage to PBPK models evaluated against the data and results from the existing SHEDS permethrin and CCA case studies.

Type: DATA
MODEL

Delivery Date (FY): 2014

(9) Beta testing of the SHED-Lite model with program partners and stake holders and publication on further model refinements.

Type: DATA
MODEL

Delivery Date (FY): 2014

(11) Web-based software tool for predicting skin absorption rate based on inherent chemical properties.

Type: DATA SOFTWARE

Delivery Date (FY): 2013

(13) A pharmacokinetic process decompositionscript to capture physiological and chemical-specific parameters for physiologically based pharmacokinetic (PBPK) models published in literature.

Type: OTHER

Delivery Date (FY): 2014

(14) A library of ADME related targets for polymorphism modeling will be created and annotated from the literature. This data will be used as part of a logical flow for predicting metabolic profiles by integrating with docking studies,2) Development of a new rapid molecular filter, similar to the prototype of PROPHET (Probabilistically Plausible Heuristic Enrichment of Targets) for descriptor based filtering of targets based on prior knowledge of binding affinity and statistics of said descriptors.3) Develop models for early life-stage parameters in support of exposure dose extrapolations and PBPK frameworks we will develop models and modify current Rapid Equilibrium Dialysis assays (RED) with alpha-fetoprotein in lieu of human serum albumin to determine embryonic plasma binding constants. This data and the in silico models derived from them will integrate with life-stage specific risk assessment in silico modeling in addition to coupling to ongoing efforts in child studies and the virtual embryo work and also for supporting PBPK modeling efforts

Type: OTHER

Delivery Date (FY): 2015

Start Date Q1 2012

End Date Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NERL: Jianping Xue, Valerie Zartarian, Kristin Isaacs, Peter Egeghy, Daniel Vallero, Rogelio Tornero-Velez, Jade Mitchell-Blackwood, Rocky Goldsmith, Cecilia Tan, Chris Grulke, Daniel Chang, Curtis Dary, Tom McCurdy, Eric Weber, Kurt Wolfe, Dalizza Colón, Hilda Solá-Soto, (Note: verify if here also or only in Task 2.3.1: Ann Pitchford, Maliha Nash, John Lin, Jay Christensen ?) NCCT: Elaine Hubal-Cohen, John Wambaugh, Woody Setzer NCEA: Linda Phillips Program Offices: OCHP: Michael Firestone, OCSPP: Niva Kremak, OPP: David Miller, Steve Nako, others TBD

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Identify the EF&T Models used by OCSPP, the environmental descriptors (e.g., temperature, pH, % soil organic carbon) required to parameterize the models for the estimation of environmental concentrations of organic chemicals and their potential transformation products, as well as web-accessible data bases (e.g., USGS National Water Quality Database) that store the necessary environmental descriptors	Scheduled: Q4 - 2012 Completed:

(Product 1) Apply D4EM (Data for Environmental Modeling) for retrieval and storage of the required environmental descriptors for subsequent parametrization of the EF&T models	Scheduled: Q4 - 2012 Completed:
(Product 1) Develop a prototype Environmental Systems Model that will provide the required environmental necessary for the parametrization of the EF&T models	Scheduled: Q4 - 2013 Completed:
(Product 2) Develop reaction libraries for reductive transformations and hydrolysis based on reaction rules developed through review of the peer-reviewed process science	Scheduled: Q4 - 2012 Completed:
(Product 2) Develop reaction libraries for photolysis and water disinfectant mediated based on reaction rules developed through review of the peer-reviewed process science	Scheduled: Q4 - 2012 Completed:
(Product 2) Develop a prototype Reaction Pathway Simulator that provides the dominant transformation pathways and products of chemicals for reductive transformation, hydrolysis, photolysis, and water disinfectant mediated oxidations	Scheduled: Q4 - 2013 Completed:
(Product 3) Finalize the design of the Environmental Fate Simulator based on the needs of OCSPP	Scheduled: Q4 - 2012 Completed:
(Product 3) Develop a prototype of the Chemical Editor that permits the entry of a chemical by chemical structure, common name or SMILES string	Scheduled: Q4 - 2012 Completed:
(Product 3) Provide a prototype Environmental Fate Simulator that links the Chemic Editor, Reaction Pathway simulator and the Environmental Systems Model to a structure-searchable database	Scheduled: Q4 - 2013 Completed:
(Product 4) Revised version of SHEDS-Multimedia v4 per 2010 FIFRA SAP recommendations, provided to OPP and other stakeholders, and posted to SHEDS website	Scheduled: Q4 - 2012 Completed:
(Product 5) Journal Publication: Quantifying Childrens Aggregate (Dietary and Residential) Exposure and Dose to Permethrin: application and evaluation of EPAs probabilistic SHEDS-Multimedia model	Scheduled: Q4 - 2012 Completed:
(Product 5) SHEDS model output results for different scenarios and analyses as requested by OPP for priority aggregate and cumulative risk assessments	Scheduled: Q4 - 2013 Completed:
(Product 5) Journal Publication: A Cumulative Exposure and Dose Assessment for Pyrethroid Pesticides (links with cumulative risk task)	Scheduled: Q4 - 2013 Completed:
(Product 6) Journal Publication: Methyl Mercury Exposure from Fish Consumption in Vulnerable Racial/Ethnic Populations: Probabilistic SHEDS-Dietary Model Analyses Using 1996-2006 NHANES and 1990-2003 TDS Data	Scheduled: Q4 - 2012 Completed:
(Product 6) Journal Publication: Evaluation of EPAs Stochastic Human Exposure and Dose Simulation (SHEDS) Model Estimates Against Measurements Data for Different Chemicals	Scheduled: Q4 - 2013 Completed:
(Product 7) Input to SHEDS-Lite development and collaboration on documented evaluation of higher tier SHEDS-Multimedia model against alternative lower tier modeling assessments	Scheduled: Q4 - 2013 Completed:
(Product 8) Report on comparison of SHEDS-Lite (ver 1) model to SHEDS-Multimedia model for permethrin and CCA case study applications	Scheduled: Q4 - 2012

(Product 9) Development and documentation of SHEDS-Lite (ver 2) model for internal Beta testing of it with program Offices	Completed: Scheduled: Q4 - 2013
(Product 11) Identify relevant literature for specific endpoint/property/metric	Completed: Scheduled: Q4 - 2012
(Product 11) Curate said entries and add chemical structures and names to endpoints	Completed: Scheduled: Q4 - 2012
(Product 11) Calculate molecular descriptors or decision tree models or biophysical models	Completed: Scheduled: Q4 - 2012
(Product 11) Generate QSAR or decision tree models or biophysical models	Completed: Scheduled: Q4 - 2013
(Product 11) Validate QSAR or decision tree models or biophysical models	Completed: Scheduled: Q4 - 2013
(Product 11) Add models and/or data to PReParE (see also 1.3.2)	Completed: Scheduled: Q4 - 2013
(Product 12) Identify relevant literature for tissue specific expression profiles	Completed: Scheduled: Q4 - 2013
(Product 12) Curate said entries into a spreadsheet or database environment	Completed: Scheduled: Q4 - 2013
(Product 13) Identify corpus of literature for all PBPK models	Completed: Scheduled: Q4 - 2013
(Product 13) Extract entire literature or abstract/titles into a database	Completed: Scheduled: Q4 - 2013
(Product 13) Use and/or develop named entity recognition methods for identifying key PBPK model terms, chemical terms and biomolecular terms from corpus	Completed: Scheduled: Q4 - 2013
(Product 14) Development of a new rapid molecular filter, similar to the prototype of PROPHET (Probabilistically Plausible Heuristic Enrichment of Targets) for descriptor based filtering of targets based on prior knowledge of binding affinity and statistics of said descriptors	Completed: Scheduled: Q4 - 2013

Division Approved Yes

CSS Developing the Scientific Understanding and Data for Exposure Processes

CSS 231 231

Kristin Isaacs
NERL
HEASD

Topic/Theme

2 Systems

Project

2.3 Metrics and Models that Define Chemical Exposures and Internal Dose

Associated Project

None

Task Description

EPA is tasked with understanding and quantifying both ecological and human exposures to large numbers of disparate chemicals and chemical classes, including agricultural chemicals, semi-volatile organic compounds (SVOCs), and a wide variety of other toxic substances present in household products. This large effort requires modeling both the spatial and temporal distribution of chemical concentrations in the environment, and (for human exposure) the behaviors that result in contact with and intake of these chemicals. EPA is developing a suite of multi-tier models to address the key sources, pathways, and exposure endpoints (ecological and/or human) for various chemicals and chemical classes. Conservative "lower tier" models that are mostly based on default assumptions and have limited spatial or temporal resolution are being developed for screening-level assessments, while "higher tier" models that account for variability and/or uncertainty in model algorithms, inputs, parameters and scenario specifications are being developed for targeted high-priority scientific or regulatory applications. However, there are critical gaps in the data and algorithms required to fully and robustly characterize exposure pathways within this multi-tier framework. The goal of this task is to identify and address these knowledge gaps and data needs. This task will seek to develop a quantitative understanding of the sources and transport mechanisms of chemicals within ecological and human environments, and to characterize the human activities that result in subsequent exposure and dose. The databases and algorithms developed under this task will inform a variety of EPA exposure, dose, and risk models, especially those developed under subsequent Tasks 2.3.2, 2.4.1, and 2.5.3.

Rationale and Research Approach

EPA is developing evaluated environmental exposure and dose models that can be used to characterize spatial/temporal variations in chemical(s) concentrations in real-world environments, to identify sources and pathways of exposure, and to estimate internal dose in targeted human and wildlife populations. These exposure models will require both input data and mechanistic algorithms describing basic exposure processes and factors, including ecological landscape properties, chemical emission and transport mechanisms, and human activity patterns. Models that simulate intake dose also require additional information describing human physiology and energy expenditure. In addition, these input data and algorithms can also inform lower-tier models that estimate exposure potential for high-throughput screening and prioritization purposes. The research approach for this Task is to address critical data and modeling gaps through four main activities: (1) Characterization of small water bodies (SWB) and other landscape features that impact the fate and transport of agricultural chemicals, (2) Characterization and predictive modeling of sources and transport mechanisms for SVOCs and other priority pollutants in indoor environments, (3) Development of new methods for tracking, quantifying, and archiving human activities, consumer behaviors, and chemical data for use in high- and low-tier modeling efforts and (4) Development of well-evaluated, physiologically-based methods for transforming human activity patterns into population estimates of energy expenditure, oxygen consumption, dietary intake, and ventilation for use in intake dose predictions. In support of Agency environmental fate and transport models such as PRZM-EXAMS, small water bodies (SWBs)

in predominantly agricultural settings in the U.S. will be identified, inventoried and characterized. This work will fill gaps in the current understanding of the distribution of SWBs in the environment. Existing geographic data, geographic information system (GIS) techniques, remote sensing (RS) imagery, and onground field verification will be utilized. The inventory will summarize statistics for SWB area, perimeter, depth, and volume. These data may be used in PRZMEXAMS to improve characterization of uncertainties in ecological exposure estimates for pesticide regulatory applications. Many of the EPAs high priority pollutants are semi-volatile organic compounds (SVOCs), including polychlorinated biphenyls (PCBs), brominated flame retardants, perfluorinated compounds (PFCs), bisphenol A (BPA), and phthalates. Currently, there exists a knowledge gap in understanding of the transport mechanisms of these compounds. SVOC source emission process and transport mechanisms in the residential environment and the relationship between transport rate and factors such as contaminant and source properties and environmental conditions will be studied via analytical and predictive methods. In addition, simulation tools for PCBs and formaldehyde will be developed. Early efforts will focus on these case studies: (1) construction of a simulation tool box for PCB emissions from caulking materials and PCB transport in buildings; (2) an indoor air quality simulation program for formaldehyde emissions from washing machines and dish washers due to the use of surfactants that contain formaldehyde-releasers. These products will support advances in source-to-concentration methods for Agency exposure models such as SHEDS-Multimedia and inform PCB research under Topic 4: Cumulative Risk. For more realistically informed near-field consumer-product chemical exposures with reduced participant burden, modern-day computing technology methods (smartphones, bar-code scanning, accelerometry, geo-tagging) will be used to develop a) chemical product inventories for homes and b) low-burden methods of data-entry of human activity diaries. An approach to map social networks with automated language parsers for codified human activity and location information to exposure relevant behaviors will be developed. A free and publicly available product chemical inventory (i.e., an MSDS database) will also be constructed and made accessible via both a web-browser interface and a smart-phone application. These efforts will aid in filling gaps in chemical product usage and human behavior for lower-tier screening and prioritization models that assess human exposure potential (an OCSPP need being addressed under Task 2.5.3). In addition, the low-burden methods for collecting human activity diaries will directly address data gaps in characterization of activity patterns and energy expenditures across life stages in a number of EPA exposure models, including SHEDS-Multimedia. Finally, robust, well-evaluated, physiologically-based methods will be developed for transforming human activity patterns in exposure models into population estimates of energy expenditure, oxygen consumption, ventilation, dietary and water intake, and resulting doses dose. This work will determine appropriate activity-specific energy expenditure distributions for daily human activities, while considering the impacts of lifestage, gender, health status, and fitness. These methods will be used in the refinement of linked human exposure - intake PBPK models for source-to-dose-to-effects investigations.

Outputs from Projects related to this task

(1) Consumer product use, emissions and other data for exposure and dose analyses (2) Factors & processes influencing pharmacokinetics and ADME of chemicals in organisms (3) Inputs and methods needed to model fate/ transport, concentrations, exposures and dose to different environmental chemicals

Expected Products

(5) Three related products to support near-field exposure assessment and integration with ACToR. 1) an integrated data-mining, data-aggregation and Quality Assurance (QA) workflow system to capture publically available MSDS (material safety data Sheets) for consumer products (for use in #2); 2) Develop a product chemical inventories MSDS database that is free and publicly available. This database will include information (ADME, product-activity-location relationships, etc.) on the largest number of chemicals for high-market share consumer products, queried from both web-browser interfaces (i.e. Safari, Explorer, Chrome, or Firefox), and accessible through a User Interface designed for smart-phones (see #3); and 3) Development of a smart-phone interface/app will also be developed for Personal Chemical Exposure Informatics curation that uses smart-phone bar-code scanning capabilities to capture product inventories. This app will conveniently enable entry and reporting of personal time-activity logs by study participants in the EPA CHAD time activity database

format. This tool will facilitate the data-entry aspect of exposure related surveys while also being used to bridge product 2 above with activity-to-product (and to chemical) relationships.

Type: DATA
DATABASE

Delivery Date (FY): 2013

(3) Geospatial databases, metadata, and manual for water body distribution, size, and depth in the Northeast and Southeast from the Inventory of Small U.S. Water Bodies to Reduce Uncertainty in EXAMS Modeling Assessments

Type: DATA
DATABASE

Delivery Date (FY): 2014

(4) Geospatial databases/metadata/manual and journal articles: for Texas and California, for western states and nationwide updates

Type: DATA
DATABASE

Delivery Date (FY): 2015

(6) Systems Reality modeling: 1) Software and publication on a code for CHAD that converts passive social networks by location (GPS) into activity location codes, and likely product uses. Also converts into personal chemical exposures from household products. This code will make use of named entity extraction (NEE) and Natural Language Processing, 2) Software and publication on a life-simulation environment that uses real-life activity patterns from the intelligent Journal Entry system and social networks, along with exposure factors (FROM EFH) product-chemical-location-activity database to simulate real-life exposures to everyday products, and provide a mechanism for exploring realistic scenarios of humans in their environment.

Type: DATA
SOFTWARE

Delivery Date (FY): 2016

(2) Geospatial databases, metadata, and manual for water body distribution, size, and depth in the Midwest from the Inventory of Small U.S. Water Bodies to Reduce Uncertainty in EXAMS Modeling Assessments.

Type: DATA
DATABASE

Delivery Date (FY): 2013

(8) Improved/new population distributions of physiological variables (height, weight, basal metabolic rates etc.) to be used directly in SHEDS and other exposure models supporting risk assessment.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(7) Methods that scale activity-specific energy expenditures relative to an individual's maximum oxygen consumption (or maximum metabolic equivalent, METS), to account for age, gender, health status, and fitness differences.

Type: OTHER

Delivery Date (FY): 2012

(9) Analytical methods and test protocols for studying the fate & transport mechanisms of SVOCs indoors. These will be utilized for a database on parameters for quantifying the fate and transport of SVOCs indoors including partitioning between sources and interior surface materials and direct contact between indoor sources and settled dust (i.e., material/source partition).

Type: DATA
DATABASE

Delivery Date (FY): 2015

(10) Simulation tools for modeling (1) PCB primary and secondary sources in buildings, (2) formaldehyde emissions from aqueous solutions, and (3) SVOC emissions and transport in buildings.

Type: DATA
MODEL

Delivery Date (FY): 2013

(1) Geospatial databases, meta data , and manuals that compare remote sensing, mapping and estimation techniques for the Midwest.

Type: DATA
DATABASE

Delivery Date (FY): 2012

Start Date Q1 2012 **End Date** Q4 2014

Cross Research Project Output Supported?
Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NERL: Rocky Goldsmith, Chris Grulke, Rogelio Tornero-Velez, Cecilia Tan, Daniel Chang, Daniel Vallero, Curtis Dary, Jianping Xue, Peter Egeghy, Jade Mitchell-Blackwood, Ann Pitchford, Tom Purucker, Maliha Nash, Chuck Lane, Ken Fritz, Kristin Isaacs, Tom McCurdy, Michael Breen, Carry Croghan NRML: Xiaoyu Liu, Zhishi Guo, Mark Mason NHEERL: Tony Olsen

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Example of methods and data for the Midwest	Scheduled: Q4 - 2012 Completed:
(Product 2) Example of methods and data for the Midwest	Scheduled: Q4 - 2012 Completed:
(Product 4) Completion of database that will include information (ADME, product-activity-location relationships, etc.) on the largest number of chemicals for high-market share consumer products	Scheduled: Q4 - 2012 Completed:
(Product 4) Identification, extraction, and curation of open-access MSDS database; creation of interface for database QA	Scheduled: Q4 - 2012 Completed:
(Product 4) Development of a version of database that is queried from web-browser interfaces (i.e. Safari, Explorer, Chrome, or Firefox)	Scheduled: Q4 - 2013 Completed:
(Product 4) Development of version of database that is accessible through a smart-phone interface	Scheduled: Q4 - 2013 Completed:
(Product 4) Development of a smart-phone interface/app for Personal Chemical Exposure Informatics curation	Scheduled: Q4 - 2013

(Product 5)Development of social network archiving methodology	Completed: Scheduled: Q4 - 2013
(Product 5)Development of named entity recognition linkage between spoken word diaries and CHAD activity and location codes	Completed: Scheduled: Q4 - 2013
(Product 6) Manuscript describing the analysis of data from the University Of North Carolina Department Of Exercise Physiology on energy expenditures in children aged 5-18 and relationships between maximal oxygen consumption and energy expenditure.	Completed: Scheduled: Q4 - 2012
(Product 6) Manuscript describing new algorithms for use in EPA exposure models based on correlating maximal oxygen consumption with activity-specific energy expenditures	Completed: Scheduled: Q4 - 2013
(Product 7) Completion of a database of matched height and weight data from NHANES appropriate for use in EPA exposure models for probabilistic sampling of simulated persons	Completed: Scheduled: Q4 - 2012
(Product 8) Evaluation of current EPA energy-expenditure algorithms with accelerometer data from academic partners	Completed: Scheduled: Q4 - 2013
(Product 9) Analytical methods and test protocols for studying the fate and transport mechanisms of SVOC, e.g., brominated flame retardants or other high priority compounds	Completed: Scheduled: Q4 - 2012
(Product 9) Information/parameters of transformation of SVOC, e.g., brominated flame retardants or other high priority compounds in house dust.	Completed: Scheduled: Q4 - 2013
(Product 10) Simulation tool box for PCBs in buildings	Completed: Scheduled: Q4 - 2012
(Product 10) Simulation program for formaldehyde emissions from aqueous solutions	Completed: Scheduled: Q4 - 2012
	Completed:

Division Approved Yes

CSS Predicting Ecological Outcomes from Exposure to Chemicals and Other Stressors

CSS 241 241

Diane Nacci
NHEERL
AED

Topic/Theme

2 Systems

Project

2.4 Systems Approaches to Assess Human and Ecological Risks

Associated Project

None

Task Description

While regulations have traditionally been based upon adverse biological effects of chemicals to individuals, environmental sustainability requires healthy populations, communities and ecosystems. Thus, more comprehensive ecological risk assessment must link chemical effects on individuals to those at increasing levels of biological complexity, and take into account the context in which chemical exposures occur, including physical stressors (e.g., habitat availability and quality) and biological factors (e.g., prey availability, predation). Integrated systems approaches can provide the necessary frameworks and mechanisms to account for relevant environmental, chemical, biological and ecological information, resulting in more efficient, comprehensive and realistic ecological risk assessments.

Rationale and Research Approach

In this task, ORD and Program Office staff will collaboratively address high priority needs for Tier II and III level ecological risk assessments that require methods to integrate environmentally realistic chemical exposures into the prediction of effects at the levels of the population, community, and ultimately, whole ecosystems. Research described in this task will culminate in the development and testing of integrated systems and their components to link chemical exposures and ecological effects. Methods and diagnostic metrics will be developed for well-studied chemicals and those of emerging concern that more accurately predict realistic spatial and temporal distributions of chemicals in various environments. The output from these environmental exposure models will be linked to ecological models that translate chemical distributions into biological and ecological outcomes. An important overarching strategy for this task will be to bring together state-of-science components into these integrated systems. Thus, significant integration and synergy will occur with CSS Biomarkers and Extrapolation topics, where molecular- and population-level approaches and tools are being developed, and the Systems Models Adverse Outcome Pathway Project (CSS 2.1), where biologically-based models linking molecular to population effects of chemical stressors are being explored. Although methods to extrapolate adverse outcomes to higher levels of biological organization are in exploratory stages of development, research proposed in this task will advance important goals for assessing ecological risks to communities and ecosystems, evolving towards the incorporation into environmental regulations of sustainability endpoints. This research will result in the development and evaluation of source-to-outcome pathways, their components and information needs to develop systems model approaches. The systems approaches being developed here will be designed explicitly to link exposure and ecological effects in a manner not currently available. While the systems approaches and components are designed to be broadly useful, application and testing of these methods will address an assortment of environments, chemicals, faunal groups considered high priority, and to fill or quantify the uncertainty associated with existing gaps as identified by Program Offices and Regions. System components and approaches will reflect current advances in ecological knowledge to better understand chemical risks, such as methods to evaluate competing risks from chemical and other stressors and the relative cost/benefit of complexity in population models. We will also advance next-generation genetic and genomic approaches for assessing risk of chemical

contaminant (e.g., pesticides) and non-contaminant (e.g., habitat fragmentation) stressors to the persistence of key aquatic populations. Individual and population level metrics will be developed using innovative molecular tools to provide information needed for training and evaluating spatially explicit models, thereby improving the realism of predictions of population level outcomes (in coordination with SSWR Goal 2, Themes 1.2 and 2.2). Systems approaches will be developed and tested using case studies that reflect high priorities and needs for the Program Office and Regions, such as a novel ecosystem modeling approach to integrate ecological effects of multiple stressors as applied to urban/residential estuaries (coordination with SSWR Question 6 project, Narragansett Bay Signature Project). This approach will link watershed-based exposures to ecological effects, e.g., evaluating existing/development of urban/residential exposure models for selected high priority chemicals of (e.g., pyrethroids, nanomaterials). Our research will also further the development and application of a spatially-explicit model (i.e., HexSim) for evaluating the risks from spatially structured chemical and non-chemical stressors on wildlife and human populations across small and large areas or regions.

Outputs from Projects related to this task

(1) Integrated systems approaches linking exposure and outcome (2) Integrated systems approaches for predicting individual, population, and ecosystem risk from complex patterns of chemical exposure

Expected Products

(1) Software, guidance describing Markov Chain estimation of survival probabilities in presence of competing risks (MCestimate) for application to human health and ecological risk case studies.

Type: DATA
SOFTWARE

Delivery Date (FY): 2013

(4) Design and recommendations for case studies that demonstrate systems models approaches to evolve from population- to community- to ecosystem-level risk assessment, and provide information on high priority chemicals.

Type: OTHER

Delivery Date (FY): 2013

(2) Guidance on evaluating the sources and magnitude of uncertainty in complex population models that for application to ecological risk assessment.

Type: OTHER

Delivery Date (FY): 2013

(6) Recommendations for the use of population models of varying complexity to produce improved, time-efficient population-level ecological risk assessments, taking into account available data, assessment endpoints, and uncertainty analyses.

Type: OTHER

Delivery Date (FY): 2016

(7) Spatially-explicit population models (including extensions of HexSim) to characterize exposures and link to ecological effects for a broad range stressors, and stressor interactions for species with varying life history strategies.

Type: DATA
MODEL

Delivery Date (FY): 2016

(3) Development of genetic and genomic tools for elucidating key metrics of exposure and effects for selected aquatic species and chemicals with recommendations for their use in AOP systems models

Type: OTHER

Delivery Date (FY): 2014

(5)Evaluation and guidance on the application to human and ecological risk assessment of statistical approaches to provide time and cost efficient assessment of competing risks through MCestimate software multiple-decrement life table analysis, and classical survival analysis

Type: OTHER Delivery Date (FY): 2016

(8) Gene-expression based indicators of exposure and effects for select pesticides translated to ecologically relevant model species

Type: DATA
MODEL Delivery Date (FY): 2016

(9) Development and evaluation of AOP models describing causal linkages between individual level chemical exposures and population-level impacts for ecologically relevant aquatic species in urban and agricultural landscapes

Type: DATA
MODEL Delivery Date (FY): 2016

(10) Guidance document providing and recommendations on systems modeling approaches to predict population, community and ecosystem risks from chemicals and other stressors of regulatory concern

Type: PUBLISHED REPORT
GUIDANCE DOCUMENT Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

TBD

External Collaborators (known or proposed)

TBD

Milestones

None

Division Approved Yes

CSS Identification of HTS Signatures for Adverse Outcomes

CSS 252 252

Matt Martin
NCCT
IO

Topic/Theme

2 Systems

Project

2.5 Screening and Prioritization for Exposure and Adverse Outcomes

Associated Project

None

Task Description

This task aims to develop predictive signatures of adverse outcomes from high-throughput screening (HTS) data being generated across many technologies, molecular and cellular targets and at different levels of biological organization. A signature is a combination of in vitro activities and other descriptors that correlate or associate with a specific mechanism, endpoint or adverse outcome. Standard machine learning and classification approaches have had limited success without deep consideration of the organization and biological context of the HTS and reference endpoint data. Therefore, this task will focus on 1) bioinformatics techniques to organize, aggregate and understand the HTS data; 2) identifying and developing classification and machine learning algorithms that generate stable, robust and validated signatures; and 3) database and informatics approaches to identify appropriate adverse outcomes to model from traditional toxicology studies, human epidemiological evidence, and other relevant sources. Validated HTS signatures will be used to prioritize chemicals for further testing or to play a role in an integrated testing strategy across multiple toxicities. HTS signatures will also provide a starting point for hypothesis generation and targeted testing. Signature generation will also help define the relevant pathways and targets to be included in systems models.

Rationale and Research Approach

The large scale generation of HTS data across hundreds of molecular and cellular targets, coupled with the vast amount of available biological information from the literature, will enable construction of complex and context-specific (e.g., organ-specific tumors, specific malformations) systems models relevant to toxicology. However, developing full-scale systems models across many organ and biological systems requires detailed understanding of the system, its components and the interaction of those components. More immediately, the vast amount of HTS data will be used to develop predictive signatures for pathways of toxicity, molecular initiating events, mode of action, apical endpoints, and adverse outcomes that can provide direct input into the chemical testing prioritization and decision making process. Mechanistic information from the scientific literature and from targeted testing efforts, in vitro and in vivo, will be required for signature validation including assays developed or run as part of Task 2.5.1. As direct associations between HTS assays and adverse outcomes are established via HTS signatures of specific pathways and mechanisms, this information will also help prioritize areas of systems modeling development. The development of a predictive signature involves four primary areas of research: 1) bioinformatics; 2) signature algorithms; 3) endpoint derivation; and 4) signature confirmation. The first research area will require the development and use of databases and other bioinformatic tools capable of identifying the molecular and cellular targets of hundreds of assays and organizing the results of those assays based on relevant biological information (e.g., gene, gene family, pathway, process). The second area of research will focus on the identification and development of classification and machine learning algorithms, as well as signature development workflows, capable of generating validated and biologically plausible HTS signatures. The third area of research involves the continued expansion of traditional toxicity data and study information, into relational databases, as well as the refinement of database techniques capable of extracting and aggregating endpoints from reference toxicity databases and scientific literature to serve as anchoring

endpoints for predictive modeling. The fourth area of research involves hypothesis-driven testing of generated signatures at various levels of biological organization to confirm their predictive capability. Using HTS assay data, predictive models will be developed for systemic toxicity, cancers, reproductive toxicity, developmental toxicity, endocrine disruption, neurotoxicity and immunotoxicity and will serve as the primary tool in chemical testing prioritization.

Outputs from Projects related to this task

(1) Prioritization of regulatory chemical inventories (TSCA21, OW21, EDSP21, and OPP21) based on endpoints for cancer, developmental toxicity, reproductive toxicity. (FY13) (2) Prioritization of regulatory chemical inventories (TSCA21, OW21, EDSP21, and OPP21) based on endpoints for systemic toxicity, developmental neurotoxicity and immunotoxicity. (FY16)

Expected Products

(3) Forward validation of ToxCastDB pathway-models and predictive signatures using data from ToxCast, Tox21 and other sources.

Type: DATA MODEL Delivery Date (FY): 2013

(4) Further refinement of signatures for developmental toxicity, reproductive toxicity and chronic/cancer using additional data from ToxCast, Tox21 and other sources.

Type: OTHER Delivery Date (FY): 2015

(5) Signature for developmental neurotoxicity using assays developed in 2.5.1.

Type: OTHER Delivery Date (FY): 2015

(6) Signature for developmental immunotoxicity using assays developed in 2.5.1.

Type: OTHER Delivery Date (FY): 2016

(7) Prioritization of chemicals on critical Program Office and EDSP lists from screening data generated in 2.5.1.

Type: OTHER Delivery Date (FY): 2016

(1) Prioritization and selection of ToxCast Phase-1 and Phase-II chemicals for the TSCA21, OW21, and OPP21 case studies based on endpoints for cancer, developmental toxicity, reproductive toxicity.

Type: OTHER Delivery Date (FY): 2012

(2) Expansion of ToxCastDB pathway-models and predictive signatures for developmental toxicity, reproductive toxicity and chronic/cancer endpoints using data on ToxCast Phase-II chemicals.

Type: DATA MODEL Delivery Date (FY): 2012

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

External Collaborators (known or proposed)

TBD TBD

Milestones

None

Division Approved Yes

CSS New Tools to Screen/Prioritize Chemicals Based on Exposure Potential

CSS 253 253

John Wambaugh
NCCT
IO

Topic/Theme

2 Systems

Project

2.5 Screening and Prioritization for Exposure and Adverse Outcomes

Associated Project

None

Task Description

This task provides required exposure science and computational tools for rapid characterization of exposure potential arising from manufacture and use of thousands of chemicals. The research is motivated by the increasing availability of high-throughput assays of biological activity identifying potential chemical hazard; similar assessment of exposure potential is required to achieve high-throughput risk assessment. The outcomes of the research will be the streamlining of available approaches for modeling exposure potential, development of a framework for incorporating factors critical in determining exposure potential into qualitative screening process, and ground-truthingto assess confidence in predictions. Resulting rapid exposure-based assessment approaches will guide further testing (e.g., the TSCA21 and EDSP21 workplans) as well inform broader sustainability metrics (including ExpoPi) for evaluating chemical alternatives.

Rationale and Research Approach

Determining the impact of chemicals on humans and ecosystems is essential to risk assessment and life cycle analysis. For humans in particular, there is a pressing need for robust analytical approaches that use a wide range of human exposure data, product use information, chemical properties, and modeled human behavior to systematically screen chemicals based on exposure potential to inform prioritization for further evaluation. The ExpoCast research program has the goal of providing required exposure science and computational tools for rapid characterization of human and ecological exposure potential arising from the manufacture and use of thousands of chemicals. This research addresses a stated need by OCSPP to be able to evaluate the safety of chemicals in the face of inadequate or nonexistent exposure data. High-throughput modeling will be conducted under ExpoCast to estimate exposure potential in order to prioritize the initial TSCA21 and EDSP21 chemical lists. Approaches for characterizing exposure potential will range from semiquantitative visualization of exposure metrics to mass-balance and consumer-scenario based quantitative modeling. Assessing exposure potential requires three scales of modeling: far-field (e.g., environmental fate and transport); near-field (e.g., direct and personal); and internal (chemical-specific pharmacokinetics). In this task, simplified approaches for modeling key determinants of exposure at each of these scales will be further developed, evaluated and applied to prioritize chemicals for further evaluation. Both measured and modeled metrics of exposure can be incorporated with other relevant chemical specific data (e.g., chemical properties) and weighted to determine graphically intuitive, exposure-enhanced ToxPi scores for chemicals based to inform further modeling, testing, and decision making. The approach provides accessible visual analytics to integrate QSAR, functional properties, source-to-concentration modeling (e.g., fugacity) results, and use and activity patterns. The ExpoCast approach is not wedded to a particular model, but rather is a framework allowing a suite of appropriate models to be used. A range of models is available to estimate exposures, but many require significant data, time, and resources to implement. Currently available models capable of quantitatively processing large volumes of chemicals have been identified by the ExpoCast modeling challenging, and ongoing evaluation will identify key information gaps in terms of both model processes and data availability. Further evaluation will include ground-truthing the predictions of different models against available exposure data. The

approaches that comprise this current state of the art largely rely on modeled fate, transport, and environmental partitioning, accounting for indirect exposure through the environment. While these fate and transport models provide the backbone for the first phase of ExpoCast, they typically neglect consumer product use and indoor emissions from articles, furnishings, and building materials direct exposures that are often of much higher intensity than indirect exposures. As part of this task EPA researchers will work with external collaborators to refine models for high-throughput prediction of exposure potential for the near-field, including the product phase of the chemical life cycle. The end result is a constantly evaluated suite of models for high-throughput prioritization of chemical exposure potential, with ground-truthing efforts to quantify model improvement. ExpoCast will provide rapid, on demand exposure-based prioritizations including exposure metrics and fate and transport modeling for chemical lists relevant to ToxCast, TSCA21, EDSP21, and other Program Office high needs.

Outputs from Projects related to this task

(1) Completion of TSCA21 workplan for 500 chemicals, including in vitro hazard potential identification, in vitro human pharmacokinetics determination, and chemical-structure-derived exposure potential modeling. (2) Completion of EDSP21 workplan for 2000 chemicals, including in vitro hazard potential identification, and chemical-structure-derived exposure potential modeling.

Expected Products

(3) Refined models for high-throughput prediction of exposure potential.

Type: DATA
MODEL

Delivery Date (FY): 2014

(1) ExpoCast high-throughput exposure predictions for prioritization of initial ToxCast, TSCA21 and EDSP21 chemicals including exposure metrics and fate and transport modeling of large chemical libraries.

Type: OTHER

Delivery Date (FY): 2012

(2) Evaluation of currently available models for high-throughput prediction of exposure potential requiring only minimal inputs with identification of key information gaps in terms of both model processes and data availability

Type: OTHER

Delivery Date (FY): 2012

(4) Further ExpoCast high-throughput exposure predictions and prioritization of additional ToxCast, TSCA21 and EDSP21 chemicals including exposure metrics and fate and transport modeling.

Type: OTHER

Delivery Date (FY): 2014

(5) ExpoCast screening for exposure potential of additional ToxCast, TSCA21 or EDSP21 chemicals per year selected from Program Office high priority lists.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

External Collaborators (known or proposed)

Potential team members include the following: NCCT: Cohen-Hubal, Gangwal, Judson, Knudsen, Setzer, Rabinowitz NERL: Egeghy, Mitchell-Blackwood, Vallero NRMRL: Bare NCEA: L. Phillips	TBD

Milestones

(Product 1) Development of methods for high-throughput exposure prioritization using existing far-field exposure models	Scheduled: Q1 - 2012 Completed:
(Product 1) Initial prioritization of ToxCast, EDSP21, and TSCA21 chemical lists with respect to exposure potential in support of Product 1	Scheduled: Q1 - 2012 Completed:
(Product 2) Evaluation of the available exposure data for high-throughput modeling	Scheduled: Q1 - 2012 Completed:
(Product 1) Evaluation of performance prioritizations using available ground-truthing data sets (e.g. NHANES)	Scheduled: Q2 - 2012 Completed:
(Product 1) Development of exposure augmentation for ToxPi visual analytics	Scheduled: Q2 - 2012 Completed:
(Product 2) Completed review of currently available high-throughput exposure models	Scheduled: Q3 - 2012 Completed:
(Product 3) Development of near field modules for high throughput exposure modeling	Scheduled: Q4 - 2013 Completed:
(Product 3/4/5) Application of new models to existing and new data sets	Scheduled: Q4 - 2014 Completed:
(Product 5) Begin OW21 (Chemical Contaminants Lists 4) workplan	Scheduled: Q4 - 2012 Completed:
(Product 4) Evaluation of performance prioritizations using available ground-truthing data sets (e.g. NHANES)	Scheduled: Q4 - 2014 Completed:
(Product 5) Evaluation of performance prioritizations using available ground-truthing data sets (e.g. NHANES)	Scheduled: Q4 - 2016 Completed:
(Product 4) Development of exposure augmentation for ToxPi visual analytics	Scheduled: Q4 - 2014 Completed:
(Product 5) Development of exposure augmentation for ToxPi visual analytics	Scheduled: Q4 - 2016 Completed:
(Product 3) Evaluation of available near field modules for high throughput exposure modeling using available ground-truthing data sets	Scheduled: Q4 - 2014 Completed:

(Product 4) Application of new models to existing and new data sets	Scheduled: Q4 - 2015 Completed:
(Product 5) Application of new models to existing and new data sets	Scheduled: Q4 - 2016 Completed:

Division Approved Yes

CSS Translation of Key AOPs into Medium- and High-Throughput Assays

CSS 251 251

Keith Houck
NCCT
IO

Topic/Theme

2 Systems

Project

2.5 Screening and Prioritization for Exposure and Adverse Outcomes

Associated Project

None

Task Description

Characterization of key cellular and molecular events for various Adverse Outcome Pathways (AOPs) can inform the generation and evaluation of medium- and high-throughput assays that are predictive of toxicity and can be used for chemical screening. This task will utilize available high-throughput assays relevant to human health in the ToxCast screening program to prioritize chemicals for more detailed and focused toxicity testing, and develop new assays targeting key AOPs for which screening platforms are currently unavailable. Chemicals of interest to EPA Program Offices (approximately 300 per year) will be screened using existing ToxCast assays and prioritized relative to other screened chemicals using statistical approaches described in Task 2.5.2: Identification of HTS signatures for adverse outcomes. Additional screening and prioritization using endocrine activity-focused assays will be completed on 1000 EDSP21 chemicals along with an accelerated screening of additional chemicals for EDSP21. Results will be provided in the form of a database which will be incorporated into the EDSP21 Decision Support Dashboard (Task 7.1.4), and will form the basis of peer-reviewed publications Guidance will also be developed for diagnosing and evaluation of endocrine disruptor-induced pathology in fish and amphibians. New assays targeting key AOPs for endocrine disruption, developmental neurotoxicity and developmental immunotoxicity will be developed or acquired and included in the suite of ToxCast screening assays as they become available. Guidance will be provided on approaches for testing volatile chemicals which are currently not compatible with existing screening methods. Finally, extramural research support will be provided towards understanding the relationship between chemical exposure and non-chemical stress on developmental neurotoxicity.

Rationale and Research Approach

Data needs for hazard identification and risk assessment have traditionally relied on tests conducted on animals. Conventional tests are costly, time consuming, and do not scale to the problem of testing thousands of chemicals. Furthermore, there are vast numbers of cellular and molecular interactions taking place at any one time in a tissue or organ. The age of molecular biology and genomic sciences has led to significant breakthroughs in understanding biological systems at a very fundamental level of organization. An outgrowth of this is the ready availability of hundreds of in vitro, high-throughput screening (HTS) assays targeting many critical molecular and cellular entities involved in toxicities. The ToxCast project uses a suite of over 500 HTS assays to screen hundreds of chemicals drawn from EPA Program Office chemical inventories. Using computational approaches, models are developed linking profiles of activity in these in vitro assays with conventional, animal toxicity endpoints. Endpoints for which models have been built to date include liver, developmental and reproductive toxicity. The goal of the ToxCast program is to use these screens to provide data to drive prioritization of chemicals with unknown toxicity for more focused study by traditional methods. In support of this goal, the utility of individual assays within the large suite will be verified by identifying links to in vivo toxicity endpoints; gaps in coverage of important AOPs identified, and assays developed and implemented to fill these gaps. The ToxCast project is currently in the second phase of chemical testing. The first phase focused on 309 chemicals with rich in vivo toxicity information available. Such data served to anchor the in vitro results to in vivo endpoints. Phase II of ToxCast,

currently underway with 700 chemicals, includes additional chemicals with known toxicities, but also many more with little or no data available. This phase will serve several purposes. It will help define the assays of utility to the program, it will help validate and extend the models developed in Phase I testing, and it will allow identification of gaps in HTS assay coverage. Such gaps will be filled through new contract offerings for the project and through development of assays targeting key AOPs. There are a number of important adverse outcomes (developmental toxicity, developmental neurotoxicity, developmental immunotoxicity) with AOPs where the molecular initiating events are unknown or the linkage between the upstream molecular events and the adverse effect is unclear. Assays for these adverse outcomes will be developed using cellbased assays focusing on key cellular events (e.g. cell proliferation) related to adverse outcomes at the tissue and organ level (e.g. decrease in brain growth). The approach will: a) identify gaps in the current set of pathways and assays available for chemical screening for developmental toxicity based on research in Task 2.1.1; b) develop mediumand high-throughput assays in vitro and in model organisms for identified gaps based on canonical signaling pathways of development and related key cellular events; c) evaluate reproducibility, reliability, and predictive ability of assays using chemicals known to affect development, including neuroand immunedevelopment (positive controls); d) evaluate predictive ability of new assays using chemicals selected based on known outcomes in vitro and in vivo (chemical test set). These assays may be implemented for screening in-house at EPA, transferred to a contractor for operations, or run at the NIH/NCTT laboratory as part of the Tox21 collaboration. As described above, the ToxCast assay suite is not a static set of assays. There will be an ongoing process of evaluating the utility of existing assays, dropping assays not of value and adding new assays for key AOPs. These assays will be used to prioritize approximately 300 chemicals per year derived from key Program Office chemical inventories. Chemicals for testing will be procured and managed as part of the ToxCast inventory and include chemical quality control. They will then be tested in the suite of assays current at that time and the data provided to prioritize them relative to other tested chemicals using the prioritization models described in Task 2.5.2. Currently, limitations exist to the high-throughput testing of volatile chemicals. Guidance will be provided on the issues and potential solutions. This will be followed by design and development of medium-throughput exposure systems with the potential for testing of such chemicals given their importance to various inventories. Another critical inventory of chemicals is the EDSP candidate chemicals. The first 1000 of these are currently being screened in a select set of ToxCast assays focused on endocrine activity. A database to hold screening results and associated data will be built to provide information to Program Offices. Included in this will be prioritization/weight-of-evidence models to help interpret the results. There will also be an acceleration of screening on additional chemicals beyond the first 1000 in the endocrine activity assays for the EDSP. A related activity will be the delivery of EDSP Tier 2 test (T2T) guidance and protocols to OCSPP including web-based guidance for diagnosing and scoring, and evaluating EDC-induced pathology in fish and amphibians. These projects should greatly increase the efficiency of achieving EDSP goals. Finally, in the longer term, there will be extramural research support through creation of new STAR Centers to develop new methods for understanding the relationship between chemical exposure and nonchemical stressors on neurodevelopmental (DNT) outcomes. Such interactions are currently poorly understood and difficult, if not impossible, to study using high-throughput screening assays.

Outputs from Projects related to this task

1) Data sets that support development of signatures of adverse outcomes of relevance to Program Offices based on endpoints for cancer, developmental toxicity, reproductive toxicity, systemic toxicity, developmental neurotoxicity and developmental immunotoxicity. 2) Data sets that support prioritization of regulatory chemical inventories (TSCA21, OW21, EDSP21, and OPP21).

Expected Products

(3) EDSP Tier 2 test (T2T) guidances and protocols are delivered, including web-based guidance for diagnosing and scoring, and evaluating EDC-induced pathology in fish and amphibian.

Type: PUBLISHED REPORT
GUIDANCE DOCUMENT

Delivery Date (FY): 2012

(1) Completion of high-throughput screening data sets on first 1000 EDSP21 chemicals, and ToxCast

Phase II chemical library.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2012

(2) Accelerated ToxCast screening data on additional chemicals beyond the current EDSP21 library; access new endocrine-related assays for EDSP21 (especially thyroid and steroidogenesis-related); validation studies on EDSP21 assays including targeted in vitro data on EDSP21 chemicals; database to manage EDSP21 data as well as data from guideline EDSP Tier 1 and Tier 2 studies; prioritization / weight of evidence methods / models for using EDSP21 data by program offices.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(4) Validated medium-throughput assays to screen and prioritize chemicals for developmental neurotoxicity.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(4) Validated medium-throughput assays to screen and prioritize chemicals for developmental neurotoxicity.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(5) ToxCast screening data generation for 300 chemicals critical to chemical program needs.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(6) Data sets for ToxCast chemicals in screening assays for AOPs identified in Task 2.1.1.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(7) Development of Medium- and high-throughput assays to screen and prioritize chemicals for developmental toxicity.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(8) ToxCast screening data on 300 chemicals per year selected from Program Office high priority lists.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2016

(9) Medium- and high-throughput assays to screen and prioritize chemicals for developmental immunotoxicity.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(10) Guidance on approaches for assessing volatile chemicals in high throughput test systems.

Type: OTHER

Delivery Date (FY): 2016

(11) Extramural research (STAR Centers) to support: New methods for understanding the relationship between chemical exposure and nonchemical stressors on neurodevelopmental (DNT) outcomes; and Identifying and exploring DNT adverse outcome pathways.

Type: EXTRAMURAL DOCUMENT
GRANT

Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported?
Maybe

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)

Potential team members include the following: NCCT: David Reif, Matt Martin, Richard Judson, Woodrow Setzer, Imran Shah, Tom Knudsen, Ann Richard NHEERL: Hunter, Chandler, Shafer, Mundy, Freudenrich, Wallace, Padnos, Padilla, Kligerman, Boyes, MacPhail, Jensen, Simmons, Luebke, Lehmann NERL: Mark Higuchi

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Completion of testing of first set of EDSP21 chemicals in assays for estrogen and androgen receptor activity, with data in the EDSP21 database. Data and interpretation will be made available to program offices through the EDSP21 dashboard.	Scheduled: Q4 - 2012 Completed:
(Product 2) Data from first set of EDSP21 chemicals in assays for estrogen and androgen receptor activity provided in EDSP21 database. Data and interpretation made available to program offices through the EDSP21 dashboard.	Scheduled: Q4 - 2012 Completed:
(Product 3) EDSP Tier 2 test (T2T) guidances and protocols are delivered to OCSPP including web-based guidance for diagnosing and scoring, and evaluating EDC-induced pathology of fish and amphibian.	Scheduled: Q3 - 2012 Completed:
(Product 4) Validated test battery for development of neural connectivity based on test set of 24 developmental neurotoxicants	Scheduled: Q4 - 2012 Completed:
(Product 4) Establish in vitro model of neuronal migration using primary neurons and neural stem cells	Scheduled: Q4 - 2012 Completed:
(Product 4) Develop cell-based markers for differentiation of neural progenitor cells	Scheduled: Q4 - 2012 Completed:
(Product 4) Validated in vitro assays for migration and differentiation using set of reference chemicals	Scheduled: Q4 - 2012 Completed:
(Product 4) Establish medium-throughput assay for assessing development of functional activity in neuronal networks	Scheduled: Q4 - 2012 Completed:
(Product 4) Validated medium-throughput assay for development of neuronal network	Scheduled:

function based on set of reference compounds	Q4 - 2013 Completed:
(Product 4) Validated zebrafish larval assay for developmental neurotoxicity using both behavioral and morphological endpoints	Scheduled: Q4 - 2012 Completed:
(Product 5) QC'ed ToxCast dataset for 700 chemicals selected from Program Office inventories for selected endpoints.	Scheduled: Q4 - 2013 Completed:
(Product 6) QC'ed ToxCast dataset(s) for Phase I and II chemicals in screening assays developed in 2.1.1	Scheduled: Q4 - 2013 Completed:
(Product 7) Validated zebrafish embryonic developmental assay for based on use of the teratogenic index	Scheduled: Q4 - 2013 Completed:
(Product 7) Develop markers for multiple differentiation outcomes in embryonic stem cells (ESC) using qNPA	Scheduled: Q4 - 2012 Completed:
(Product 7) Establish assays for gastrulation as a more sensitive developmental endpoint in the medium-throughput ACDC assay	Scheduled: Q4 - 2013 Completed:
(Product 8) QC'ed ToxCast dataset for 300 chemicals selected from Program Office inventories for selected endpoints.	Scheduled: Q4 - 2014 Completed:
(Product 9) Establish breeding colony of transgenic zebrafish expressing markers for development of the hematopoietic and immune systems	Scheduled: Q4 - 2012 Completed:
(Product 9) Develop novel co-culture system to assess immunotoxicity based on antigen presentation in 3A9 T cells and Ch27 B cells	Scheduled: Q4 - 2012 Completed:
(Product 9) Demonstrate utility of the transgenic zebrafish model for assessment of immunotoxicity with set of positive control chemicals	Scheduled: Q4 - 2012 Completed:
(Product 9) Establish human dendritic THP-1 cell line for the assessment of immunotoxicity based on IL-8 production	Scheduled: Q4 - 2013 Completed:
(Product 10) White paper on testing of volatile chemicals in HTS assays	Scheduled: Q4 - 2012 Completed:

Division Approved Yes

CSS Integrated Multi-Tiered Systems Toxicology Approach to Determine and Predict Health Effects of Nanomaterials

CSS 261

261

Kevin Dreher
NHEERL
EPHD

Topic/Theme

2 Systems

Project

2.6 An Integrated Systems Approach to Assess and Predict the Toxicity of Engineered Nanomaterials and their Applications

Associated Project

None

Task Description

This Task examines the health effects of Agency-relevant and commercially available engineered nanomaterials (NMs). The proposed research employs an integrated multi-tiered systems toxicology approach to examine NMs over a life-cycle based (cradle to grave) perspective while overcoming many challenges associated with conducting nanotoxicology research. It incorporates priority-ranked research while employing a horizontal and vertical testing matrix for NMs to identify inherent chemical properties regulating their reactivity, biological interactions, uptake and toxicity. An integrated multi-tiered systems toxicology approach allows research to respond to the immediate needs of Agency stakeholders while conducting fundamental research to address longer-term research needs for NM health/environmental effects. Research products will include contemporary and translatable toxicity endpoints, methods, approaches, models, and guidelines to: i) assess, rank and predict with greater certainty acute and chronic NM health effects using high-throughput and high-content testing methods; ii) inform green nano-chemistry/engineering and identify alternative NMs; iii) identify adverse outcome pathways (AOPs), their molecular initiating and key events and dose-response metric(s) for specific NM health/environmental effects; and iv) identify susceptibility factors influencing NM deposition, fate and toxicity.

Rationale and Research Approach

Rationale: Currently, over 1,000 products containing engineered NMs have reached the market place. Already, NMs have been detected in treated-release waste water and ambient air, indicating that public and environmental exposures to NMs are possible. Concurrently, there is a high degree of uncertainty regarding potential NM health/environmental effects and the adequacy of existing harmonized test guidelines to assess NM toxicity. Finally, there are significant challenges associated with assessing the health/environmental effects of NMs due to their diversity in number and applications, novel physicochemical properties, ability to translocate and accumulate in multiple organs following various routes of exposure and consequently, their potential to elicit a broad range of toxicities. Research Approach: Task 2.6.1 examines the health/environmental effects of Agency-relevant commercially produced NMs organized across a matrix with a vertical (several NM classes: metals: Ag, Ag-silica; metal oxides: TiO2, CeO2, CuO, CuCO3; carbon based: MWCNT) and horizontal (several NMs within the same class varying in physicochemical properties such as: size, length, crystal structure, composites and coatings) design. This research approach will identify the inherent chemical properties (ICPs) regulating NM reactivity, biological interactions, ADME and toxicity. An integrated multi-tiered systems toxicology approach will assess NM health effects as described in ORDs externally reviewed Nanomaterial Research Strategy, EPA 620K/K-09/011, June 2009 (www.epa.gov/nanoscience). This approach consists of three tiers: 1) NM physical and chemical characterization; 2) NM cellular and non-cellular alternative testing; and 3) NM in vivo toxicity testing. This multi-tiered approach is consistent with the National Academy of Science, National Research Council, Toxicity Testing in the 21st Century (Tox21) and several nanotoxicology workshop reports (Oberdorster et al., Particle and Fiber Toxicology, 2005; Warheit et al., Inhalation Toxicology, 2007;

Balbus et al., Environ. Health Perspect. 2007). Tier 1 NM Physical and Chemical Characterization - All NMs employed in health/environmental effects testing will undergo physicochemical analyses. This characterization is critically important because: i) NM physicochemical data provided by commercial sources can be inaccurate; ii) accurate physicochemical data are required for nano QSARs and identification of ICPs and dose-response metric(s) responsible for specific NM health effects. To the extent possible, Tier 1 research will also include physicochemical analysis following NM exposure in order to determine the extent of uptake, deposition and fate in Tiers 2 and 3. Tier 2 Cellular and Non-cellular Alternative Testing to assess, screen and rank NM toxicity. This research will include non-cellular, cellular and organ perfusion approaches described in prioritized CSS projects 091, 123, 129, 166 and 030. Cellular models will assess the toxicity of several organ systems (hepatic, pulmonary, immune, gastrointestinal, dermal, neuronal, cardiovascular and gastrointestinal). This systems toxicityapproach is based on the ability of NMs to distribute throughout the body following various routes of exposure impacting diverse cellular targets and organ systems. Tier 2 studies will characterize NM cellular uptake and distribution, examine effects on cell growth/cytotoxicity, indicators of cellular stres and altered function and develop in vitro models to assess the ability of NM to penetrate specific biological barriers (e. g. skin-blood, lung-blood, GI-blood, blood-brain). Tier 2 research will utilize available ToxCast high-throughput assays relevant to human health to prioritize NMs for more focused toxicity testing in Tier 3 and compare conventional vs., alternative nanomaterials to inform safe and sustainable materials development. Identification of NM mode of action (MOA) and adverse outcome pathways (AOPs) will be conducted in Tier 2 research. A longer-term effort under Tier 2 will be to develop models to determine the impact of susceptibility factors and life stages has NM health/environmental effects. Research performed under Tier 2 will also include non-cellular assays to evaluate the inherent NM reactivity (e.g., reactive oxygen/nitrogen production or depletion, antioxidant depletion, protein modification) and binding properties of NMs as these properties may play significant roles in their environmental and biological interactions, deposition, fate and toxicity as well as assist in the development of nanoQSAR models. Tier 3 NM In Vivo Toxicity Testing this research will examine the in vivo toxicity, health/environmental endpoints, and AOPs of NMs screened and prioritized in Tier 2. This will allow a means to identify credible translatable NM health/environmental effects endpoints, AOPs and alternative methods/approaches which predict with greater certainty NM in vivo toxicity. Tier 3 research will also be employed to address specific targeted human health effects needs of Agency offices such as cardiovascular toxicity assessment of carbon nanotubes (must do CSS002 project) and the toxicity and fate of Ag, nanoAg-silica, CuO, CuCO3 nanoparticles following oral and/or inhalation exposures. Research performed under Tier 3 will also provide methods and guidance on generating and characterizing NM aerosols and dispersion for in vivo toxicity testing. Integration: The multi-tiered systems research approach to assess NM health effects will progress in an iterative manner with Tier 2 and 3 informing each other. This approach allows the assessment of NMs toxicity at multiple levels to identify validated alternative test methods, ICPs and AOPs predictive of NM in vivo toxicity and provide a means to address stakeholder needs in a timely manner.

Outputs from Projects related to this task

(1) Life Cycle based effects of nanomaterials (2) Credible translatable alternative test methods, guidelines, and endpoints predictive with high confidence NM in vivo toxicity (3) Mechanisms of injury, mode of action and AOP for HTP and HCS methods development (4) Nano-QSARs and inform green nano chemistry/application/engineering (5) Best current in vitro and in vivo methods for tier testing of NMs provided to Offices (6) AOPs identifying common, sensitive and susceptible biological receptors predictive of adverse human and ecological outcomes

Expected Products

(1) Recommendations on best current in vitro, in vivo and non-cellular test methods, best practices and guidelines to expose, screen, rank as well as identify hazardous properties, AOPs and inherent reactivity of nanoparticles: TiO2 and CeO2 (high priority); Ag and nanoAg/silica composite.

Type: OTHER Delivery Date (FY): 2013

(2) ToxCast HTS assay data to classify nanomaterials based biological activity, providing ability to

evaluate conventional and alternative nanomaterials to inform safe and sustainable materials development.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(3) Guidance on application of in vivo endpoints/assays, best practices and to assess carbon nanotube cardiovascular toxicity following pulmonary exposure.

Type: OTHER

Delivery Date (FY): 2013

(4) Data, models, test methods and best practice describing the acute health effects of carbon nanotubes and identification of alternative methods to predict them.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(5) Data, models, test methods and best practices describing subchronic health effects of selected Agency relevant NMs and identification of alternative methods to predict them.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(6) Data, models and methods identifying key factors that affect susceptibility and mitigate NM human health toxicity including environmental factors and material characteristics (Integrated with 2.6.1(12)).

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(7) Guidance on the use of health and ecological NM toxicity information derived from molecular, cellular, organ and whole animal/in vivo levels to identify: i) dose metric(s) of exposure to response; ii) AOPs and ADME with their ICPs for development of high throughput and high content testing methods; and iii) best practices and test methods for the use of alternative models, tiered testing and in vivo tests to assess their toxicity (Integrated with 2.6.1).

Type: OTHER

Delivery Date (FY): 2016

(8) ToxCast HTS assay data generated on approximately 30 materials per year and prioritization of materials based on the screening data.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2016

Start Date Q1 2012

End Date Q1 2016

Cross Research Project Output Supported?
Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NERL: K. Rogers, R. Willis, R. Zepp NRMRL: T. Tolaymat, S. Al-Abed NHEERL: S. Diamond, C. Andersen

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Selection, acquisition, independent analysis and multi-tiered (1, 2, and 3) toxicity testing of CeO2 and TiO2 nanoparticles	Scheduled: Q3 - 2012 Completed:
(Product 1) Selection, acquisition, independent analysis and multi-tiered (1, 2, and 3) toxicity testing of Ag nanoparticles and Ag nanoparticle-silica composite	Scheduled: Q4 - 2012 Completed:
(Product 1) Product (1) Selection, acquisition, independent analysis and multi-tiered (1, 2, and 3) toxicity testing of CuO and/or CuCO3 nanoparticles	Scheduled: Q2 - 2014 Completed:
(Product 2) Synthesis and use-equivalence testing of alternative nano-silver products	Scheduled: Q3 - 2013 Completed:
(Product 2) Generation of testing data set for alternative nano-silver and conventional nano-silver products in ToxCast assays	Scheduled: Q3 - 2013 Completed:
(Product 3) Literature review reporting the cardiac and vascular effects of single and multi-wall carbon nanotube and selection of health endpoints to evaluate the cardiovascular toxicity	Scheduled: Q3 - 2012 Completed:
(Product 3) Characterize the cardiac and vascular health effects following pulmonary exposure of rats to multi-wall carbon nanotubes displaying various lengths and degree of dispersion/aggregation	Scheduled: Q1 - 2013 Completed:
(Product 4) Selection, acquisition, independent analysis and multi-tiered (1, 2, and 3) toxicity testing of carbon nanotubes	Scheduled: Q1 - 2013 Completed:
(Product 5) Selection of NPs for subchronic toxicity studies as well as in vitro and in vivo models, endpoints and approaches for subchronic and repeated exposures	Scheduled: Q4 - 2013 Completed:
(Product 5) Conduct subchronic toxicity testing of selected NPs and identify Determine the best models, endpoints and approaches to detect and predict subchronic toxicity of various NPs	Scheduled: Q1 - 2014 Completed:
(Product 6) Using selected in vitro and in vivo models and endpoints identify how and what susceptibility factors influence the toxicity of selected NPs	Scheduled: Q1 - 2015 Completed:
(Product 7) Collection, integration, and analysis of toxicity data from Alternative Toxicity Testing and Targeted In vivo Toxicity Testing with physiochemical properties, AOPs and mechanisms of injury for CeO2 and TiO2 NPs	Scheduled: Q3 - 2013 Completed:
(Product 7) Collection, integration, and analysis of toxicity data from Alternative Toxicity Testing and Targeted In vivo Toxicity Testing with physiochemical properties, AOPs and mechanisms of injury for Ag and Ag-silica NPs	Scheduled: Q3 - 2013 Completed:
(Product 7) Collection, integration, and analysis of toxicity data from Alternative Toxicity Testing and Targeted In vivo Toxicity Testing with physiochemical properties, AOPs and mechanisms of injury for CuO and/or CuCO3 NPs	Scheduled: Q1 - 2015 Completed:
(Product 7) Collection, integration, and analysis of toxicity data from Alternative Toxicity Testing and Targeted In vivo Toxicity Testing with physiochemical properties, AOPs and mechanisms of injury for MWCNT NPs	Scheduled: Q4 - 2015 Completed:
(Product 7) Determine the extent to which susceptibility factors impact data analysis relating toxicity to inherent properties for CeO2 and TiO2, Ag and Ag-silica, CuO	Scheduled: Q1 - 2016

and/or CuCO3 NPs and MWCNT	Completed:
(Product 8) Selection and acquisition of materials for testing FY14	Scheduled: Q3 - 2013 Completed:
(Product 8) Selection and acquisition of materials for testing FY15	Scheduled: Q3 - 2014 Completed:
(Product 8) Selection and acquisition of materials for testing FY16	Scheduled: Q3 - 2015 Completed:

Division Approved Yes

CSS

Systems-Based Approach for Assessing Hazard and Risk of Manufactured Nanomaterials and Non-Human Species and Ecosystems

CSS 262

262

Steve Diamond
NHEERL
MED

Topic/Theme

2 Systems

Project

2.6 An Integrated Systems Approach to Assess and Predict the Toxicity of Engineered Nanomaterials and their Applications

Associated Project

1.2 Nanomaterial-Specific Inherency Issues

Task Description

This task focuses on the ecotoxicology of manufactured nanomaterials (particles or fibers that have at least one dimension between 1 and 100 nm). These materials are of immediate concern to regulatory offices because they exhibit properties not observed in their traditional bulk form, are being developed and incorporated into products at a rapid rate, and require novel and non-standardized test approaches due to their particulate nature. In addition, due to their small size alone, these particles may be taken up and translocated via mechanisms very different from those typical of truly soluble substances. The inherent properties that determine toxicity might also differ significantly from traditional, soluble chemicals, for example surface plasmon activity that occurs only at the nanoscale and allows surface electrons to behave in unpredictably. These unique properties have the potential to elicit system-level responses at every level of organization, from the molecular/sub-cellular to the ecosystem (for example carbon or nutrient cycling). Many of these responses could be mitigated by variation in size or other material attributes that can be manipulated during production (e.g. using green chemistry principles). This Task is designed to serve two broad purposes. The first is to develop methods for working with a broad range of nanomaterials with the immediate goal of providing test guidance to regulatory Offices, primarily OCSPP (FY12/13 Products). The second is characterizing and quantifying toxicity of various nanomaterials in freshwater, marine, and terrestrial systems to provide Offices with basic toxicity information (FY12/13 Products) but also to develop a basis for investigating chronic toxicity, mechanisms of action, toxic pathways, and initiating events, and ultimately to develop predictive tools to preclude extensive plant and animal testing.

Rationale and Research Approach

Understanding how nanomaterial exposure and toxicity differ from soluble chemicals is critical for elucidating their ecological hazard and risk, and for determining whether their behaviors and effects across levels of biocomplexity (individuals, populations, communities, intact ecosystems), are inherently different from traditional chemicals. It has been well-established that, because of their particulate and fibrous nature, nanomaterial exposure occurs via colloidal suspensions of insoluble particles rather than true solutions, and that these suspensions typically behave in a manner that is not addressed in standardized test methods. The particles agglomerate (change size), settle, and exhibit continuously-changing surface properties. This level of variability is also seen in dry testing (e.g., terrestrial systems) even where wet suspensions are not used in development of exposure media. Preliminary research suggests that it is generally not possible to limit variation in critical nanomaterial properties over the duration of most tests and that characterization at relatively frequent intervals (relative to soluble chemicals) is necessary to fully quantify exposure. For example, titanium dioxide nanoparticles tend to agglomerate over 24-hour renewal periods in aquatic media, changing in average particle size from 200 nm to 2000 nm. This behavior results in settling of material from the water column and an order-of-magnitude reduction in the total number of particles present, both factors that greatly reduce exposure. Understanding these behaviors allow us to identify susceptible targets in ecosystems, for example benthic communities in aquatic and marine systems. In addition to

presenting profound challenges for regulatory testing, these behaviors are also not easily documented and typically require methods and approaches that have yet to be developed or standardized. These challenges are made more complex by the nearly unlimited variation in the as-produced form of nanomaterials, including particle size (and size distribution), surface coating, material combinations (e.g. CdSe quantum dots), functionalization (e.g. addition of hydroxyl or carboxyl groups), and pre-application "packaging" (e.g. stabilization in matrices that will be removed during product incorporation). All of these modifications can affect the behaviors described above. Our research approach will be to focus initially on developing methods for preparing test media and approaches for characterizing nanomaterials in media during testing. This effort will address media development for freshwater, marine, and terrestrial test systems, each of which presents novel problems, including highly variable agglomeration behavior due to varying salinity and the lack of methods for detecting nanomaterials in terrestrial and other complex media (e.g. sediments). Initially, these efforts will focus on TiO2, nano-silver, and carbon nanotubes. These materials are representative of metal oxides, metals, and carbon-based materials, respectively, and may provide a basis for broad application of developed methods across these material classes. Tested media preparation approaches will include stirring, sonication, and use of solvents, dispersion, and stabilizing agents. In the latter case, naturally-occurring stabilizing agents such as dissolved organic carbon will be tested, as this will also provide insight into nanomaterial behavior in natural environments. Characterization approaches will include particle sizing (dynamic laser-light scattering),fractionation, near infrared fluorescence detection, visible and electron microscopy (with back-scattering detection for material identification), as well as material extraction and isolation methods. The hypothesis underlying this effort is that nanomaterials will require novel testing approaches. Our aim is to develop these approaches and to provide guidance to Offices on how nanomaterial testing should be undertaken to accurately represent the potential hazard of nanomaterials and their applications. Concurrent with our media-development efforts, we will characterize and quantify the toxicity of the materials being studied. These efforts are closely aligned, as nanomaterial behavior in media is changed by the presence of organisms (due to alteration of ionic strength, pH, and other critical parameters that are affected by or derived from organism exudates). The necessity of developing test media with organisms present allows for immediate preliminary assessment of toxicity and identification of potential test endpoints. The refinement of media preparation methods, material characterization approaches, and exposure-response relationships will occur simultaneously. This approach will also provide the opportunity to continuously identify and evaluate material characteristics (inherent properties) that are most closely related to organism responses, e.g. particle size effects on the surface area available for material-target interactions or release of soluble, toxic species. The responses of organisms will be used to infer, and guide the further investigation of modes and mechanisms of action and the toxic events that initiate adverse outcome pathways. For a subset of tested materials and systems, ingestion, uptake, and food-chain exposure will be investigated, and where possible, other effects on ecological processes such as benthic community interactions or nutrient cycling (in simple, model exposure systems) will be identified and characterized. A likely focus will be investigating the role of reactive oxygen species that are likely to be produced on the surface of many nano-scale materials, and are well-understood relative to initiating events and AOPs. The hypothesis underlying this effort is that nanomaterials will exhibit some level of toxicity and that organism responses might be unique relative to soluble chemicals. Our aim is to provide data to regulatory Offices on toxicity and eco-toxicity of selected nanomaterials, and to identify and characterize modes and mechanisms of action where possible. These near-term efforts (FY12/13) will focus on a limited number of nanomaterials (carbon nanotubes, nano-silver, and nano-TiO2). These materials are the focus of ongoing research and were selected based on Office input, development of the ORD Nanomaterials Research Strategy and ORD involvement in OECD efforts. A goal of this effort to develop a suite of techniques, approaches, and methods that allow ORD to rapidly address immediate Office needs across a broad range of nanomaterials. These efforts will be undertaken in close collaboration and integration with CSS, Systems Task 2.6.1 and Tasks in the CSS Inherency Topic. These efforts will also provide the basis for out-year (FY14/15/16) deeper investigation of chronic and indirect effects, material and environmental properties that mitigate toxicity or other effects (and inform green and sustainable nanomaterial development), and full modeling of dosimetry, and identification and development of alternate assays that might accelerate testing and avoid material-by-material plant or animal testing. The scope of these out-year efforts is dependent on levels of funding and other forms of support and

the results of the near-term efforts described above.

Outputs from Projects related to this task

1) Approaches for standardized testing of nanomaterials 2) Quantify acute toxicity of selected nanomaterials 3) Understanding of inherent properties of modifications that mediate specific nanomaterial toxicity or other effects 4) Identify mechanisms of action for nanomaterials, AOPs, and suggestions for development of alternative and rapid throughput assays 5) Suggestions for the development of models linking inherent properties and adverse outcomes (e.g. QSARs for nanomaterials)

Expected Products

(1) Guidance on best available methods and approaches for eco-testing and characterization of selected nanomaterials.

Type: OTHER Delivery Date (FY): 2013

(2) Data on toxicity of selected nanomaterials, including exposure-response models, uptake, distribution, modes of action, AOPs, and initiating events for non-human species and ecological processes.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2015

(3) Exposure-response models describing identified chronic and/or early life-stage toxicity of selected nanomaterials on marine, freshwater, and terrestrial systems.

Type: DATA
MODEL Delivery Date (FY): 2015

(4) Identification and quantification (where possible) of the indirect effects of selected NMs on ecological processes including nutrient and carbon cycling.

Type: OTHER Delivery Date (FY): 2014

(5) Description of factors that mitigate or alter nanomaterial toxicity including product characteristics (e.g. coatings, production methods, etc.) and environmental factors (e.g. dissolved organic matter, sunlight, etc.) (Integrated with 2.6.1(6)).

Type: OTHER Delivery Date (FY): 2015

(6) Data and guidance on the relative importance of food chain exposure and related toxicity compared with other routes of exposure.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2014

(7) Guidance on the use of ecological NM toxicity information to identify: i) dose metric(s) of exposure to response; ii) AOPs and ADME with their ICPs for development of high throughput and high content testing methods; and iii) best practices and test methods for the use of alternative models, tiered testing and in vivo tests to assess their toxicity (Integrated with 2.6.1(7))

Type: PUBLISHED REPORT
GUIDANCE DOCUMENT Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NERL: K. Rogers, R. Willis, R. Zepp NRMRL: T. Tolaymat, S. Al-Abed NHEERL: K. Dreher

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Develop and refine methods for media preparation for acute toxicity testing for selected nanomaterials	Scheduled: Q4 - 2012 Completed:
(Product 1/2/3) Conduct acute toxicity testing of TiO2, n-Ag, and SWCNT in selected systems	Scheduled: Q3 - 2012 Completed:
(Product 2/3/4/5) Identify factors that mediate or affect toxicity of selected nanomaterials	Scheduled: Q3 - 2015 Completed:
(Product 2/3/6) Quantify food chain transfer and toxicity of SWCNT in a model marine system	Scheduled: Q2 - 2013 Completed:
(Product 2/3/4/7) Identify indicators (e.g. genomic) of effects of TiO2 on selected plant species	Scheduled: Q4 - 2012 Completed:
(Product 2/3/5) Develop exposure response models for identified effects (ongoing over life of the project, 2012 - 2016)	Scheduled: Q4 - 2016 Completed:
(Product 7) Refinement and validation of dose metrics, dose-response relationships, AOPs, initiating events, biomarkers, and screening tools for selected nanomaterials in freshwater, marine, and terrestrial systems.	Scheduled: Q4 - 2016 Completed:

Division Approved Yes

CSS

Evaluate Susceptibility

CSS 313 313

Steve Edwards
NHEERL
ADH

Topic/Theme

3 Biomarkers

Project

3.1 Developing and Evaluating Approaches and Tools to Improve Biomarker Research in Risk Assessment and Management Processes

Associated Project

None

Task Description

TBD

Rationale and Research Approach

TBD

Outputs from Projects related to this task

Use of biomarkers/bioindicators for predicting greater or more resistant adversity at similar dose

Expected Products

TBD

Type: OTHER Delivery Date (FY):

Start Date Q4 2016 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

TBD

External Collaborators (known or proposed)

TBD

Milestones

None

Division Approved Yes

CSS

Evaluate approaches and tools for using biomarkers of exposure to better understand and predict how environmental exposure(s) results in internal dose(s)

CSS 311 311

Cecilia Tan
NERL
HEASD

Topic/Theme

3 Biomarkers

Project

3.1 Developing and Evaluating Approaches and Tools to Improve Biomarker Research in Risk Assessment and Management Processes

Associated Project

None

Task Description

This task is focused on developing approaches and supporting data and tools to link biomarkers of exposure to exposures. Herein, biomarkers of exposure are defined as measurements of native chemicals, metabolites, or products of molecular interactions in biological media that reflect exposure to exogenous chemicals. Given the appropriate dosimetry models and supporting exposure data, these biomarkers can be quantitatively linked to exposures. By establishing the linkage between exposure and biomarkers, it enables our capability to reconstruct exposure conditions that led to the observed biomarker results. This task contains two major components. The first component is the development of a workflow for reconstructing potential exposures to exogenous chemicals using biomarker measurements, biomonitoring study data, and available exposure information such as pathways and routes (short term). This workflow will be applied to address specific requests from Program Office and Regions to reconstruct exposures from biomarkers of Agency interest to support risk assessment and risk management decisions (medium term). The second component of this task is the collection of exposure and biomarker data for supporting exposure reconstruction of high priority chemicals. For example, targeted field and laboratory studies can be conducted to collect data such as exposure/biomarker time profiles, human activity patterns, or chemicals metabolism rate. In addition, an extendable panel of biomarkers will be developed to provide information on the characteristics of biomarkers (e.g., LOD, analytes, analytical methods), their appropriateness for exposure reconstruction (e.g., specificity, sensitivity), and other relevant exposure/toxicity data (e.g., exposure routes, link to ToxCast).

Rationale and Research Approach

Historically, biomarkers of exposure have been used as de facto evidence of chemical exposure and absorption. Given the growing number of population-based biomonitoring surveys (e.g., CDC NHANES), there is an escalated interest in using biomarkers to reconstruct exposures for supporting risk assessment and risk management decisions (NRC 2006, GAO 2009). There are two main reasons for reconstructing exposures from biomarkers. One reason is that the traditional risk assessment paradigm and the resulting estimates of safe exposure are based on measures of administered dose or exposure concentration. As a result, biomarker measurements need to be converted to exposure concentrations for comparison to a safeexposure level to put biomarker results in a health risk context. The other reason is that without proper linkage between biomarkers and exposures, one cannot identify susceptible individuals, especially those who do not have high biomarker results but may have a health effect associated with their exposures. Predicting a biomarker concentration from an exposure concentration is a deterministic process that leads to a unique solution. On the other hand, reconstructing exposure concentrations from biomarker results is an inverse problem that has multiple, or even infinite, solutions. Examples of the potential uncertainty in reconstructing exposure concentrations include the source of exposure (oral, dermal, inhalation), frequency and duration of exposure event, time of biomarker sample relative to exposure event, or

variability of physiology in the population. To constrain estimates of exposures, exposure sources/pathways/routes, human activities, and pharmacokinetic information need to be integrated with biomarker results in the exposure reconstruction process. A workflow will be developed in this task to guide the integration of various types of data using pharmacokinetic models. Several statistical approaches for solving the inverse problem (e.g., Bayesian approach) will also be developed and included in this workflow. Some of these approaches will be implemented in a software package that is publicly available. The workflow will be developed using data-rich chemicals, such as chlorpyrifos and carbaryl, so that it is possible to identify sources of uncertainty and characterize their impact in the exposure reconstruction process. The workflow for exposure reconstruction will be applied not only to analyze biomarkers of Agency interest, but also to evaluate whether a specific biomarker and existing data on exposures and pharmacokinetics are sufficient/suitable to reconstruct exposure. In the case where additional data are required, targeted field or laboratory studies will be conducted to collect these data. In addition, analytical methods can be developed for the identification of unique biomarkers of exposure dosed rodents tissues. Once these biomarkers are identified from the animal studies, matched serum/urine from general population human subjects (in collaboration with NIEHS) or identified highly exposed human subjects will be used as a proof of concept to screen for any identified biomarkers. Priority will be given to the development of non-invasive human biomonitoring methods when possible, to insure greater study participation and a broader range of age classes included. These data can be used by the Program Offices and Regions to prioritize the various sources of exposures, reduce uncertainty in risk assessment, and ultimately design effective mitigation and monitoring strategies. Besides the exposure reconstruction workflow, an extendable panel of exposure biomarkers will be developed and annotated to provide a knowledge-base for current biomarkers. This panel will include the characteristics of biomarkers (e.g., limit of detection, analytes, analytical methods, biological or environmental matrix, species, robustness of assay), their appropriateness for exposure reconstruction (e.g., sensitivity, specificity, validity, variance components), as well as other relevant exposure/toxicity data (e.g., pharmacokinetic, toxicity, exposure scenarios, relevant co-exposure). In addition to capturing published information on each biomarker, biomarkers relevant for Agency risk assessment will undergo internal evaluation and optimization of the assays. This information will be included in the annotation information stored for each biomarker. In addition, this effort will result in internal expertise for the measurement and analysis of each biomarker and subsequent inclusion of the biomarker in future field studies conducted by the ORD. Over time, this will result in a much richer dataset for interpreting these biomarkers than the individual publications often done in isolation which are currently the norm.

Outputs from Projects related to this task

(1) Holistic approaches to foster a better understanding of relationship between exposure metrics and biomarkers, allowing for potential to reconstruct exposures from biomarkers. (2) Improved methodologies for exposure and dose estimates by integrating biomarker data with supporting information/data (e.g., exposure factors and pharmacokinetic behaviors) into predictive models.

Expected Products

(1) Method for reconstructing potential exposures to pesticides and other chemicals using ancillary exposure information, biomonitoring study design, and biomarker data.

Type: OTHER Delivery Date (FY): 2012

(2) Web-based software tool to conduct reverse dosimetry probability calculations for estimating exposure concentrations that are likely to have produced the observed biomarker concentrations.

Type: DATA
SOFTWARE Delivery Date (FY): 2012

(3) Panel of novel and existing biomarkers of exposure for high priority and high-interest emerging chemicals.

Type: OTHER Delivery Date (FY): 2016

(4) A workflow for characterizing the uncertainty in exposure/dose reconstruction process.
Type: OTHER Delivery Date (FY): 2016

(5) Application of exposure/dose reconstruction approaches for estimating exposure or uptake dose for high priority chemicals.
Type: OTHER Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)
NERL: Jon Sobus, Mark Strynar, Marsha Morgan, Kathleen Holm NHEERL: Stephen Edwards

External Collaborators (known or proposed)
TBD

Milestones

(Product 1) Present a generalizalble method, using carbaryl as an example, for reconstructing exposures from urinary biomarker data in a peer-reviewed journal	Scheduled: Q3 - 2012 Completed:
(Product 1) Present a workflow, using chlorpyrifos as an example, for linking biomarker results to potential exposure pathways/routes using available exposure/pharmacokinetic data in a peer-reviewed journal	Scheduled: Q4 - 2012 Completed:
(Product 1) Present a framework and study design to reconstruct human exposures to non-persistent chemicals (i.e., pyrethroids) in residential setting using urinary biomarkers in a peer reviewed journal	Scheduled: Q3 - 2012 Completed:
(Product 1) Develop a draft database that contains all Ex-R study data (i.e., ancillary and chemical concentration data)	Scheduled: Q4 - 2012 Completed:
(Product 1) Present an analytical method, using perfluorinated precursor compounds as examples, for the extraction and metabolite identification in dosed rodent tissues	Scheduled: Q4 - 2012 Completed:
(Product 1) Present results from screening human matched serum/urine to identify unique metabolites in a peer-reviewed journal	Scheduled: Q4 - 2013 Completed:
(Product 2) Develop a software for conducting reverse dosimetry calculations for estimating exposures from biomarker data. The software will be posted on EPA website for public use	Scheduled: Q3 - 2013 Completed:
(Product 3)Assemble a list of biomarkers of exposure for inclusion in initial panel in collaboration with PO and Regional partners	Scheduled: Q3 - 2012 Completed:
(Product 3) Define annotation information to be gathered for each biomarker in collaboration with PO and Regional partners	Scheduled: Q3 - 2012 Completed:
(Product 3) Gather published annotation information for biomarker panel	Scheduled: Q4

	- 2013 Completed:
(Product 3) Initiate internal evaluation for a subset of the biomarker panel	Scheduled: Q4 - 2013 Completed:
(Product 3) Incorporate annotation information into a database in collaboration with Dashboard and SHC projects	Scheduled: Q4 - 2013 Completed:
(Product 3) Make biomarker panel with annotation information available to PO and Regional partners	Scheduled: Q4 - 2013 Completed:

Division Approved Yes

CSS

Link Bioindicators to Key Events in AOPs

CSS 312 312

Steve Edwards
NHEERL
ADH

Topic/Theme

3 Biomarkers

Project

3.1 Developing and Evaluating Approaches and Tools to Improve Biomarker Research in Risk Assessment and Management Processes

Associated Project

None

Task Description

This task is focused on bioindicator discovery, evaluation, and interpretation. The term bioindicator is used in lieu of biomarker of effectto emphasize a critical link between effects biomarkers resulting from this task and a key event from a mode of action or adverse outcome pathway (AOP) leading to an adverse outcome in humans or an ecological species. By explicitly linking our effects biomarkers to these AOPs, we hope to increase the diagnostic capability of the bioindicators for endpoints of regulatory interest. We will evaluate published biomarkers both in terms of assay robustness and for diagnostic capabilities. For biomarkers of Agency interest, we will improve/replace the assays as needed to provide the appropriate sensitivity, quantitation accuracy, specificity for key event, etc. We will also establish distributions for these biomarkers in normal individuals/populations as well as sensitive subpopulations as needed. If published biomarkers of Agency interest do not have an AOP linkage to a regulatory endpoint, we will establish these linkages and determine the quantitative relationship between the biomarker and its corresponding key event in the AOP (thereby converting it to a bioindicator). In cases where AOPs of regulatory interest are missing key bioindicators, we will identify novel bioindicators from accessible matrices (e.g. blood, urine, breath) and develop robust assays for these bioindicators. Studies will also be designed to develop AOPs and bioindicators simultaneously for those cases where no biomarker or AOP exists for an important endpoint of regulatory interest. While evaluation of diagnostic capability in human epidemiology or ecological field studies would be performed in task 3.2.1, investigators from our task will be involved in those studies, and information from those studies will be incorporated into our biomarker annotation information.

Rationale and Research Approach

The state of the science for biomarkers of effect is insufficient to meet Agency needs. Many published reports of changes in endogenous biomarkers from human or ecological field studies lack an explicit relationship to an adverse outcome of regulatory concern. To incorporate the information from these reports into an Agency risk assessment, we need this information. In cases where this information is lacking, we need the ability to generate the information or clearly articulate the additional information needed to allow others to address the potential concern. We plan to address this Agency need through the development and annotation of a panel of effects biomarkers/bioindicators representing the most commonly used or cited biomarkers from the published literature. By making this information readily available to risk assessors, we will improve their ability to make and communicate decisions that incorporate published biomarker studies. We will also improve our ability to quickly launch a biomarker-based study in response to an Agency need. However, improving the use of existing biomarkers is not enough. There are many laboratory-based hazard assessments where no known biomarkers exist that can be measured in the target organisms or measurable biomarkers have no quantitative linkage with the endpoint of concern. This makes it impossible to evaluate the human/ecological relevance of the lab-based finding. In cases where this lack of data results in an unacceptable uncertainty in the risk assessment, we will identify novel biomarkers linked to the corresponding AOP and evaluate these biomarkers for their quantitative relationship with the endpoint

of concern. This would then facilitate the evaluation of Agency decisions for the desired impact in the population of concern. The central focus of this task is to develop and annotate a panel of diagnostic bioindicators linked to adverse outcomes of Agency concern. This panel will include endogenous biomarkers from the published literature with specific interest in those related to chemical toxicology and those included in ongoing biomonitoring efforts such as NHANES. In addition to capturing published information on each biomarker, biomarkers relevant for Agency risk assessment will undergo internal evaluation/optimization of the assays. This information will be included in the annotation information stored for each biomarker. In addition, this will result in internal expertise for the measurement of each biomarker and subsequent inclusion of the biomarker in future field studies conducted by ORD. Over time this will result in a much richer data set for interpreting these biomarkers than the individual publications often done in isolation that are currently the norm. Over time, the biomarkers from this panel will be converted to bioindicators by linking them to key events in AOPs, which should result in diagnostic improvements. Human biomarker chemicals are rarely unique compounds stemming from particular exposures or health state. Instead, biological media generally contain all chemicals, both environmental and endogenous, albeit at differential levels depending on the individual and other meta-data. As such, it is crucial to understand what defines normal(or unremarkable) levels in the healthy population and which measurements can be considered statistically different and therefore probative at some confidence level. The evaluation portion of this task will strive to develop measurement methods, to analyze various biological media samples (blood, breath, urine), and to establish distributions in the general population for suites of related biomarker compounds. Furthermore, the statistical results will be further partitioned based on parameters such as gender, ethnicity, age group, and phenotype (height, weight, etc.). Once such parameters are established, probative biomarkers can be identified in observational/cross-sectional, case-control, and chamber studies of sub-populations. The use of proteomic technologies such as mass spectrometers (e.g., triple quadrupole, MALDI, and LTQ-Orbitrap), and high-density protein arrays enables the discovery and identification of protein biomarkers in complex biological media. This approach provides a quantitative measurement of any changes occurring in the protein profile between exposed and unexposed individuals to identify appropriate targets for high-throughput assay development and application. Protein profiles collected at different time points can also facilitate the study of toxicity-specific changes for bioindicator identification. Non-protein biomarkers can also be identified through the use of mass spectrometry and array techniques. The designation of candidate biomarkers by analytical methods can lead to the elucidation of key biochemical pathways and mechanisms of toxicity. Once specific biomarkers or their relative concentrations (e.g. patterns) are identified as remarkable by in vivo human studies with sub-populations, the next step is to develop environmental or biochemical pathways that are the underlying basis of relevantstatus. If they can be shown to be along a metabolic route leading to a statistically plausible adverse health outcome, they can then be identified as bioindicators. This discovery activity will incorporate recently developed graphical, pharmacokinetic, and stochastic modeling techniques for complex biomarker data that uses both empirical measurements and co-collected meta-data. Since the ultimate goal will be to convert all effect biomarkers in our panel into bioindicators, this task will emphasize the linkage to key events or toxicity pathways within an AOP. These studies will be performed in laboratory animal studies to provide simultaneous measurements of bioindicators from accessible matrices and direct measurements of key events within the target tissue. Development of biomarker assays for humans and other species of concern would proceed in parallel as described above, however, to ensure that the bioindicator is suitable for field studies. An ongoing proof of concept study looking for blood biomarkers of stress reactivity in response to a series of pesticides (including carbamates, OPs, pyrethroids, and others) and their relationship to neurological alterations is being completed. Following the completion of this initial proof of concept, this approach will be extended to include early blood biomarkers of cancer. The role of systemic inflammation in cancer and neurotoxicological AOPs will be the central theme of this study, as that increases the likelihood of identifying circulating markers mechanistically linked to target tissue events. Precise chemicals and cancer or neurotoxicological endpoints for this study have not been determined. Targeted testing of ToxCast compounds could be considered as well as chemicals or endpoints to meet specific program or regional needs. Since the goal of these studies is to demonstrate the utility of this approach, chemicals with solid data linking them to the outcome of interest are required. Some knowledge of the mechanistic basis is preferred, but a full AOP is not required. Linkage of potential blood biomarkers to the AOP will be accomplished

through extensive characterization of the target tissues from the in vivo studies as well as in vitro work as needed to verify the hypothesized AOP. Future studies could then apply this same approach to identify bioindicators linked to AOPs for additional endpoints of concern identified and prioritized by program/regional partners. Finally, there is a need for computational approaches to integrate these data across platforms, model systems, and temporal/spatial dimensions. To address this, we will apply extant exposure information to guide development and use of toxicity information for improved risk-based decisions. Case-studies will be developed for high interest, data-rich compounds to explore and demonstrate approaches for linking individual, population, and ecosystem level exposure information (e.g. NHANES biomonitoring, observational exposure, epidemiological, NIEHS exposure biology data) with ToxCast bioprofiling data and other publicly available genomic information (e.g., available through CTD). Approaches to be explored include extending network analysis to span multiple levels of biological organization. Application of novel techniques to capture critical determinants of exposure for translation from controlled in vitro systems to the open system of real-world human-environment interaction will also facilitate evaluation of alternatives for sustainable chemical management.

Outputs from Projects related to this task

(1) Develop and maintain a state of the art panel of biomarkers of effects for use by risk assessors and researchers. (2) Link biomarkers to key events in an adverse outcome pathway and thereby improve the diagnostic capabilities of the biomarkers in the panel.

Expected Products

(1) Panel of existing bioindicators evaluated for diagnostic capability. Evaluation will include robustness of the assay, bioindicator distribution in healthy and affected populations, and predictive capability for adverse outcomes.

Type: OTHER Delivery Date (FY): 2016

(3) Expand panel of biomarkers as needed and improve the diagnostic capabilities by explicilty linking biomarkers to key events in AOPs.

Type: OTHER Delivery Date (FY): 2016

(5) Extend systems science methodology to link hazard information to outcomes of chemical exposures at the individual/population level relevant for decision making.

Type: OTHER Delivery Date (FY): 2016

(2) Novel bioindicators from an accessible matrix (blood) predictive for a targeted adverse outcome (functional neurological changes) within an AOP framework.

Type: OTHER Delivery Date (FY): 2016

(4) Expand annotations for the biomarker panel to include information on behavior of the biomarker across species.

Type: OTHER Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

External Collaborators (known or proposed)

Potential team members include the following: NHEERL: Carl Blackman, Brian Chorley, David Herr, Ginger Moser, Jeff Ross, Dina Schreinemachers, Sheau-Fung Thai, Marc Williams, Charles Wood NERL: Tzippora Kormos, Joachim Pleil, Matthew Stiegel, Mark Strynar, Jeanette Van Emon NCCT: Elaine Cohen-Hubal Cincinnati: David Lattier	TBD

Milestones

(Product 1) Assemble list of biomarkers of effect for inclusion in initial panel in collaboration with PO and Regional partners	Scheduled: Q3 - 2012 Completed:
(Product 1) Define annotation information to be gathered for each biomarker in collaboration with PO and Regional partners	Scheduled: Q3 - 2012 Completed:
(Product 1) Summary document on The Current State of Science in Epigenetic Biomarkers to provide scientists in the program offices with the latest developments in the epigenetics research field as it relates to cancer	Scheduled: Q3 - 2012 Completed:
(Product 1) Webinar on The Current State of Science in Epigenetic Biomarkers	Scheduled: Q4 - 2012 Completed:
(Product 1) LC-MS/MS analysis of urinary metabolites of exogenous chemical exposures to assess toxicologically relevant exposure	Scheduled: Q4 - 2012 Completed:
(Product 1) Method development of pharmacokinetic models for assessing liver function using bio-indicator hexafluoroisopronanol in exhaled breath	Scheduled: Q4 - 2012 Completed:
(Product 1) Gather published annotation information for biomarker panel	Scheduled: Q2 - 2013 Completed:
(Product 1) Incorporate annotation information into a database in collaboration with Dashboard and SHC projects	Scheduled: Q3 - 2013 Completed:
(Product 1) Make biomarker panel with annotation information available to PO and Regional partners	Scheduled: Q3 - 2013 Completed:
(Product 1) Methods development for measurement of human protein adducts using novel immunochemistry instrumentation and sandwich ELISA technique	Scheduled: Q4 - 2013 Completed:
(Product 1) Establishing ranges and distributions of endogenous human biomarkers using NMR, GC-MS, LC MS-MS and immunochemistry analyses of blood, breath and urine	Scheduled: Q4 - 2013 Completed:
(Product 2) Finish consolidated data analysis of multi-analyte and hormone data from 5 chemicals	Scheduled: Q4 - 2012 Completed:
(Product 2) Present results for OCSPP and other interested POs/Regions to begin a dialog for how the information could be used in Agency decision making	Scheduled: Q3 - 2013 Completed:

(Product 2) Present results in peer-reviewed journal paper	Scheduled: Q4 - 2013 Completed:
(Product 5) Use case-examples for high interest, data-rich compounds that explore and demonstrate approaches for linking individual and population level exposure information.	Scheduled: Q4 - 2014 Completed:
(Product 5) Evaluation of systems science methodology to identify key features of human-environment relationships relevant for characterizing health impacts of chemical exposures at the individual/population level.	Scheduled: Q4 - 2016 Completed:
(Product 1) Comparison of protein arrays and flow cytometric methods for pesticide biomarker determination	Scheduled: Q4 - 2013 Completed:

Division Approved Yes

CSS Facilitate the Development and Use of a Biomarker-Based Systems Platform

CSS 321 321

Jon Sobus
NERL
HEASD

Topic/Theme

3 Biomarkers

Project

3.2 Using Biomarker/Bioindicator Data to Develop, Evaluate, and Utilize Integrated Systems Models to Support Risk Assessment/Management Decisions

Associated Project

None

Task Description

Recent decades have witnessed tremendous growth in the measurement and assessment of chemical biomarkers. Small targeted research studies, often based on highly-exposed occupational cohorts, have focused on identifying predominant exposure pathways and identifying individuals at increased risk of harm. In parallel, broad screening-level studies (e.g., NHANES) have utilized biomarker measurements to evaluate population exposure trends, potential exposure/health differences between sub-populations, and responses to regulatory actions/decisions. Data interpretation methods can be quite different based on study design (e.g., longitudinal vs. cross-sectional). Yet, there is mounting interest in extrapolating analysis strategies from targeted longitudinal studies to large cross-sectional data sets (e.g., NHANES). While useful under certain conditions, there is often uncertainty on the appropriate application of these strategies, and the proper interpretation of the quantitative results. As such, the first objective of this research project is to develop clear guidance for the use and interpretation of existing biomarker data; this guidance is critical for proper utilization of biomarker data in regulatory decision-making. As data gaps and uncertainties will be highlighted, a second objective is to perform the science necessary to fill data gaps for high priority chemicals of regulatory interest. This work will assemble products under 3.1.1 (developing exposure-biomarker linkages) and 3.1.2 (indentifying bioindicators of AOPs) into a systems-modeling platform centered on biomarkers. Using this platform, biomarker and bioindicator measurements will be used to: 1) predict human exposure levels for comparison to reference values (e.g., RfD); and 2) evaluate the suitability of existing reference levels (generally based on animal toxicity data with uncertainty factors) using human in vivo biomarker-bioindicator associations as observed in case studies. Considering these primary objectives, this research is specifically designed to strengthen the role of biomonitoring in regulatory decision-making. While the specific applications of this task are for human health risk assessment and management, the approaches could be applied for ecological species as well.

Rationale and Research Approach

Biomarkers are valued for their abilities to integrate exposures through all relevant routes and to forecast health impairments prior to full disease onset. Despite these benefits, a biomarker measurement by itself may only be evidence of an exposure event or a snapshot of an individuals internal (biochemical) environment. To become fully utilized in regulatory decision-making, biomarkers should be analyzed over time and in concert with other metrics of exposure and health; for example, measurements of environmental media and from medical/pathological examinations, respectively. In large-scale cross-sectional studies, however, biomarker measurements may have little or no corresponding exposure or health data, thus limiting applications in regulatory decision-making. Therefore, the main objectives of this research are to give guidance on the use and interpretation of existing data, as well as the collection and analysis of new data, to meet the specific needs of Agency risk assessors/managers. The primary challenges for meeting these goals are as follows: 1) identifying the most pressing research needs (i.e., individual chemicals or toxicity endpoints of greatest concern);

2) identifying available tools to address research needs (e.g., existing biomarkers, analytical methods, biomarker databases, data analysis tools); 3) identifying and communicating gaps in available tools and resources; 4) designing and performing research to fill critical knowledge gaps; and 5) extrapolating knowledge from priority research endeavors to support additional analyses. The research under this project, combined with that described under CSS project 3.1, is designed to address each of these challenges. In the following section, specific aims of biomarker research are given to address each challenge. Specific Aim 1: Prioritize research needs The first step for CSS projects 3.1 and 3.2 is to identify chemicals and toxicity endpoints that are of highest interest/concern to the Agency. This must be done in accordance with the needs of the program/regional offices, and the capabilities of the Biomarkerstask teams. Specific Aim 2: Identify available biomarker tools and research needs Based on prioritized research needs from specific aim 1, existing biomarkers (used either within or outside of the Agency) will be identified and annotated in a biomarker knowledgebase. This work will be performed under CSS tasks 3.1.1 and 3.1.2, and will directly contribute to this task (3.2.1) Specific Aim 3: Identify and communicate gaps in available tools and resources Work under specific aim 3 will develop clear guidance for the use and interpretation of existing biomarker data, as identified under specific aim 2. Several methods have been proposed for utilizing existing cross-sectional biomarker data (e.g., NHANES) to predict human exposures and health risks. Specific methods include linear/non-linear/logistic regression modeling, derivation of human biomonitoring assessment values (e.g., biomonitoring equivalents), stochastic exposure-dose modeling, and exposure reconstruction. Critical assumptions of biomarker data and model parameters may be made (either explicitly or implicitly) when using any of these methods. As such, results may not be robust quantitative estimates for use in risk assessment/management decisions. This research will therefore critically evaluate individual methods, under certain data availability scenarios, for their ability to support regulatory decision-making. Case studies (utilizing simulations) will demonstrate the applicability and utility of each method for evaluating biomarker data against established reference values (e.g., RfDs). Multiple scenarios (e.g., non-persistent vs. persistent chemicals, urinary vs. blood biomarkers, etc.) will be evaluated to articulate requirements of models and data (e.g., percent of observations above detection limits) to adequately support exposure and risk evaluations. In parallel, methods for better utilizing biomonitoring data in evaluating reference values will be developed using the same case studies. Results of these scenario-based simulations will be the basis for a set of guidelines and best practices for interpreting existing biomarker data. Specific Aim 4: Design and perform research to fill critical knowledge gaps The methods introduced under specific aim 3 are often best used given repeated observations of biomarkers, exposure indicators, and health state. Since these data are seldom available in large cross-sectional studies (e.g., NHANES), predictions of exposure and risk are subject to uncertainty. In cases where the level of uncertainty is unacceptable, targeted research can be performed to fill critical data gaps. ORD has recently developed a biomonitoring framework designed to support exposure and risk assessments. This framework is the foundation for a systems-modeling platform centered on biomarkers. Using this framework as a starting point, case studies will be performed on target populations to better inform exposures to, and health risks from target chemicals. A primary focus of these case studies will be the simultaneous evaluation of exposure-biomarker linkages (as indentified in CSS task 3.1.1), and biomarker-bioindicator linkages (as identified in CSS task 3.1.2). Results from these targeted biomarker evaluations will be used to inform analyses of extant and new data, as described below. Specific Aim 5: Extrapolate knowledge to support new analyses Computational tools (see specific aims 3 and 4) and supporting biomonitoring knowledgebases (see specific aim 2) will be integrated into an accessible platform (potentially through Dashboards) to aid in generating exposure and risk estimates (along with associated uncertainties), and tracking responses to Agency mitigation efforts. These tools will be built to accept varying levels of information to allow predictions for data poor chemicals as well as data rich chemicals. Guidance will be provided to users, via documentation and personal support from ORD, allowing for informed use of the tools. This final component of research will advance and standardize methods for biomarker data interpretation (particularly NHANES), and provide unequivocal guidance for prospective biomonitoring studies of target chemicals. Ultimately these combined research efforts (specific aims 1-5) should enable risk assessors/managers to quickly determine, given any biomarker dataset, the available methods for data analysis, the most appropriate method(s) to be used for exposure and risk inference, and the approximate uncertainty associated with any biomarker-based prediction.

Outputs from Projects related to this task

(1) Biomarker-based predictive models to handle data rich and data poor chemicals, and provide risk estimates, uncertainties on those estimates, and methods to reduce uncertainty. (2)Tools built upon biomarker-based predictive models to evaluate & compare the potential impacts of risk management activities.

Expected Products

(1)Best practices for integrating existing biomonitoring data into risk assessment demonstrated with a case study. Report will give generalizable guidance for: Calculating exposure, dose, and target dose; calculating uncertainty; predicting risk; and identifying opportunities for mitigation

Type: OTHER Delivery Date (FY): 2013

(2) Computational tools and supporting biomonitoring knowledgebases (from Biomarkers Project 1 and 2 [above]) will be integrated into an accessible platform (potentially through Dashboards) to aid in generating exposure and risk estimates (along with associated uncertainties), and tracking mitigation responses.

Type: DATA SOFTWARE Delivery Date (FY): 2015

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)	**External Collaborators (known or proposed)**
NERL: Cecilia Tan, Joachim Pleil, Kathleen Holm NHEERL: Steve Edwards, Rory Conolly, Dina Schreinemachers, Marc Williams	TBD

Milestones

(Product 1) A review of available methods for integrating NHANES biomonitoring data into the chemical risk assessment process	Scheduled: Q1 - 2013 Completed:
(Product 1) A report of predicted quantitative uncertainties associated with these methods based on model simulations using various data availability/quality scenarios	Scheduled: Q3 - 2013 Completed:
(Product 1) A report of best practices for data analysis based available methods and uncertainty predictions	Scheduled: Q4 - 2013 Completed:
(Product 2)Case study on target population to fill critical data gaps observed using current biomarker analysis strategies	Scheduled: Q4 - 2015 Completed:
(Product 2)Synthesis and evaluation of computational platform using data from biomarker case study	Scheduled: Q4 - 2015 Completed:
(Product 2)Software- or web-based platform for aiding exposure and risk estimation, supporting regulatory decision-making, and tracking mitigation efforts, using available	Scheduled: Q4 - 2016

biomarker data and supplementary information Completed:

Division Approved Yes

CSS Utilize the Biomarker-Based Systems Platform for Decision-Making

CSS 322 322

Steve Edwards
NHEERL
ADH

Topic/Theme

3 Biomarkers

Project

3.2 Using Biomarker/Bioindicator Data to Develop, Evaluate, and Utilize Integrated Systems Models to Support Risk Assessment/Management Decisions

Associated Project

None

Task Description

TBD

Rationale and Research Approach

TBD

Outputs from Projects related to this task

Refine risk estimates

Expected Products

TBD

Type: OTHER Delivery Date (FY): 2016

Start Date Q4 2016 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

TBD

External Collaborators (known or proposed)

TBD

Milestones

None

Division Approved Yes

CSS

Data and Methods for Identifying Real-World Stressor Combinations; Methods and Models for Exposure Assessment for Mixtures of Stressors

CSS 411

411

Mike Tornero
NERL
HEASD

Topic/Theme

4 Cumulative Risk

Project

4.1 Developing, Refining, and Evaluating Data, Methods, Models, and Approaches across the Source-to-Outcome Continuum for Cumulative Risk Assessment/Management

Associated Project

None

Task Description

It is widely appreciated that humans and wildlife are exposed simultaneously or sequentially to complex mixtures of multiple chemicals from multiple sources (outdoor and indoor air, drinking water, food, dust, soil, personal care products, and consumer products). They are also exposed to non-chemical stressors/factors that may result in adverse outcomes for the exposed individual/population. Identification of highly exposed or at-risk populations remains difficult due to the absence of sufficient knowledge regarding the composition of real world chemical mixtures, when and where these mixtures come into contact with the receptor(s), related receptor susceptibility factors, and the interactions with non-chemical stressors. Typically, these issues have been addressed by application of uncertainty factors in the risk assessment process. Better characterization of the real-world total exposure experiences for humans and wildlife is required to inform relevant mixtures toxicology research (Task 4.1.2 below) and to generate exposure data to improve cumulative risk assessment and risk management decisions. This research will provide the data and methods to reduce these exposure gaps and uncertainties. The research results will also inform the research being planned in Systems Projects 2.3 and 2.4.

Rationale and Research Approach

Rationale: Chemical regulations and toxicological research have historically emphasized the characterization and regulation of individual toxic chemicals, including pesticides; however, several regulations (FQPA, SDWA, amendments to CAA) recognize the need to safeguard the public and wildlife (especially ESA) against the cumulative effects of chemicals. Full exposure and hazard assessments are resource intensive; more efficient methods, tools and approaches are needed. Methodologies have been developed to evaluate interactions among chemicals and to develop health indices for cumulative effects of mixture constituents, most often for chemicals acting by a common mechanism. Similar exposure tools are needed for identifying and/or predicting relevant real-world environmental mixtures and/or groupings of chemicals. Without data reflective of real-world environmental exposures, including the environmental concentrations of the chemicals comprising the mixture, toxicologists can only evaluate hypothetical mixture combinations. Furthermore, there is a need to consider the population demographics or sub-populations exposed to such mixtures. The National Research Council noted that current cumulative risk assessment practices do not adequately incorporate non-chemical factors and other aspects of vulnerability. This research provides tools to predict key mixtures of chemical (primary focus for CSS) and non-chemical stressors (collaboratively with SHCRP) in the environment (including near field) and to inform the prediction of the potential hazard of the mixture. Approach, developing/evaluating chemical co-occurrence algorithms: The traditional model for chemical risk assessment proceeds in a series of steps consisting of: i. hazard identification, ii. dose-response analysis, and iii. exposure assessment. This works well for single-chemical risk assessment since (ii) and (iii) are largely independent of each other. However, in the case of cumulative risk assessment, it is necessary to identify chemical mixtures that are readily

available for human and wildlife exposure, which manifest in similar health outcome(s), and which should be grouped together in dose-response evaluations. This requires exposure assessors and toxicologists to work collaboratively. It will also require the identification of non-chemical factors which can interact with environmental exposures to alter the development of adverse outcomes. In this task, predictive exposure tools will be developed and evaluated for identifying and prioritizing mixtures of chemicals in the environment (spatially and temporally). The results of this research will be used to inform the development of predictive tools to rapidly assess the potential hazard for the key high exposure mixtures identified (Task 4.1.2) along with research being planned in Systems Projects 2.3 and 2.4. The results from past and current environmental, epidemiological, and exposure studies need to be inventoried and examined to develop an environmental/exposure/biomarker chemicals database for understanding real-world environmental concentrations and potential exposures to chemical mixtures. As an example, two promising studies which should be further explored to generate pesticide exposure co-occurrence are: (1) American Healthy Homes Survey (AHHS): a national study of residential pesticides; and, (2) Child Care Center Survey (CCCS): a national health survey of child care centers. These collaborative studies (HUD, CPSC, EPA) represent nationally representative sampling of multiple chemicals, provide valuable data on chemical co-occurrence patterns, and include covariate demographic data. This data will also allow laboratory experimentation to determine the roles of these covariates in modifying the biological responses to environmental exposures. By focusing on key events in adverse outcome pathways developed in the CSS Systems Models project, chemical and non-chemical factors can be identified, grouped and prioritized for cumulative risk assessment or further research. Preliminary evaluations of the CCCS survey data, using the surface wipe residue data for the pyrethroids class of insecticides, have indicated specific co-occurrence patterns for these chemicals (not all chemicals in the class co-occur). This information has been used to derive a chemical mixture for testing purposes; the proportions of the chemicals reflect the CCCS environment. Several pharmacokinetic and neurotoxicity studies have been conducted based on this mixture in support of the previous ORD/OPP Pyrethroids Cumulative Risk Assessment collaborative research. The data from these studies will provide the basis for further elaborating linked exposure-dose models for multiple chemicals for assessing cumulative risk. A key aspect of this task is to understand how environmental survey data and other auxiliary data sources (e.g, usage information) can help to inform model development (exposure-dose models) for cumulative risk.

Outputs from Projects related to this task

(1) Predictive tools for identifying and prioritizing real-world mixtures of chemical (CSS priority) and non-chemical (SHCRP priority) stressors (environmental, residential, SES, diet, etc.) based on: Sources (including commercial and consumer products); Surrogate exposure and hazard indices; and, Toxicity of chemical or mixtures. (2) Examination and optimization of prototypical AHHS and CCS survey study designs to document real-world mixtures spatially and temporally.

Expected Products

(1) Linked SHEDS and PBPK modeling system for supporting FQPA cumulative risk assessments.

Type: DATA
MODEL

Delivery Date (FY): 2012

(2) Algorithms for investigating chemical co-occurrence patterns for identification of environmentally-relevant mixtures for informing toxicity testing and CRA using pesticide and survey data from AHHS and CCS for a case study.

Type: OTHER

Delivery Date (FY): 2013

(3) A toolbox for organizing and input of extant exposure, screening, product, and survey data for analysis of chemical co-occurrence patterns.

Type: OTHER

Delivery Date (FY): 2015

Start Date Q1 2012 **End Date** Q4 2015 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NERL: Kathleen Holm, Peter Egeghy, Nicolle Tulve, Valerie Zartarian, Chris Grulke, Curtis Dary, Kent Thomas NCCT: Jimena Davis, Woody Setzer, Elaine Hubal (co-occurrence algorithms) OPP: Edward Scollon CSPP: TBD

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Develop Bayesian Calibration Methodology for single chemicals	Scheduled: Q1 - 2012 Completed:
(Product 1) Extend Bayesian PBPK Calibration methodology for single chemicals to mixtures (cumulative)	Scheduled: Q2 - 2012 Completed:
(Product 1) Develop SHEDS methodology for multimedia aggregate chemical assessment	Scheduled: Q1 - 2012 Completed:
(Product 1) Extend SHEDS aggregate methodology to mixtures (cumulative)	Scheduled: Q3 - 2012 Completed:
(Product 1) Evaluate methodology with a cumulative case study	Scheduled: Q3 - 2012 Completed:
(Product 2) Develop co-occurrence algorithms	Scheduled: Q3 - 2012 Completed:
(Product 2) Apply co-occurrence algorithms to CCC study	Scheduled: Q4 - 2012 Completed:
(Product 2) Apply co-occurrence algorithms to AHHS study	Scheduled: Q1 - 2013 Completed:
(Product 2) Consult with NCCT on feasibility of evaluating identified mixtures in high-throughput assays and/or in silico models	Scheduled: Q4 - 2012 Completed:
(Product 2) Submit report on CCC and AHHS case study findings	Scheduled: Q2 - 2013 Completed:
(Product 3) Consult with office/region stakeholders on purpose, utility, structure, and outputs	Scheduled: Q1 - 2013 Completed:
(Product 3) Determine algorithms to include in the toolbox	Scheduled: Q2 -

	2013 Completed:
(Product 3) Determine types of survey data to manage with the toolbox	Scheduled: Q3 - 2013 Completed:
(Product 3) Develop the toolbox and evaluate performance.	Scheduled: Q4 - 2015 Completed:

Division Approved Yes

CSS Methods and Models for Assessing Hazards/Effects Resulting from Real-World Exposures to Multiple Stressors

CSS 412 412

Jane-Ellen Simmons
NHEERL
ISTD

Topic/Theme

4 Cumulative Risk

Project

4.1 Developing, Refining, and Evaluating Data, Methods, Models, and Approaches across the Source-to-Outcome Continuum for Cumulative Risk Assessment/Management

Associated Project

None

Task Description

This task is focused on the development and implementation of improved toxicological methods and models for assessing the human and ecological health impact of environmentally relevant exposures to multiple contaminants or stressors. Historically, the toxicology of mixtures and interactions has been largely observational with investigators using their personal preferences or professional judgement to select mixtures and cumulative exposures for evaluation. This research task is motivated by the need to develop a coherent strategy so that the limited available toxicology research resources are focused on the mixtures and combined exposures that are expected to have the largest impact on human health outcomes. The outcomes of the research will be efficient methods for prioritizing the vast numbers of possible mixtures and cumulative exposures for testing and improved methods and models to assess their health impact. This will result in an improved understanding of those mixtures and cumulative exposures that are of greatest potential concern with regard to human health risk, informing risk management and risk reduction efforts.

Rationale and Research Approach

Humans are theoretically exposed to vast numbers of chemicals, chemical mixtures and non-chemical stressors. There are 84,000 chemicals currently on the TSCA inventory, with approximately 1,000 new chemicals introduced into commerce each year. Without even considering non-chemical stressors, it is clear that toxicological evaluation, even if limited to in vitro screens, cannot begin to evaluate all possible combinations of these chemicals, in particular when considering such variables as sequence of exposure or differential sensitivity due to life stage or life style. The problem is compounded when it is acknowledged that very few methods and models for toxicological assessment of the health risk from chemical mixtures have moved beyond use solely by the developer. Thus, there is an imperative need to develop hazard and effects methods and models suitable for adoption by a wide array of users. Further, there is a need for transparent and objective mechanisms to focus attention on those mixtures that are likely to be of greatest concern. One aspect of this research is designed to quantitatively consider a number of factors that may impact the ability to detect deviations from additivity. For component-based approaches, there has been essentially no consideration, to date, for how such variables as model selection, model fit to the single chemical data, the expression of dose and variability of the data affect the ability to detect deviations from additivity. By using existing data sets and generating new data where needed, we will provide the first evaluation of these factors, considering not only whether they make a detectable difference, but determining the magnitude of the difference. From this research, improvements in experimental design and analysis methods and approaches will result, resulting in increased confidence that non-additivity, when detected, is real and is not an artifact of the method or model selected. Because it will not be possible to experimentally test all mixtures and combined exposures, a second aspect of this task is the development of the next generation of predictive toxicology tools. Given the overwhelming number of theoretical mixtures, these predictive tools are needed to determining which chemical mixtures warrant toxicological

evaluation. We will work toward methods for developing contaminant groupings for defined mixtures and complex mixtures. Defined mixture groupings will be based on such factors as data indicating they affect a common target organ or that in HTS assays, they trigger the same adverse outcome pathway (collaboratively with CSS Systems Models). The methods that we will create to develop contaminant groupings will be extended to methods that are capable of prioritizing chemical mixtures for testing. The extensions will require incorporation of exposure data and knowledge (see Task 4.1.1) as well as dose-response information. For complex mixtures, the groupings are intended to cluster groups of chemicals within the complex mixture, decreasing the complexity of the model. Once logical groupings are developed and priority mixtures are identified, it is important to be able to predict their effect. This requires development of a set of flexible and accurate predictive models for estimation for toxicity of contaminant groups that allow for addition and deletion of contaminants and varied specification of chemical concentrations. Once predictive models are developed that estimate of the effects of mixtures, experimental data will be collected to determine how accurately these models predicting the experimental mixtures data. The results of this task will provide improved methods and models for assessment of the human and ecological health impact of exposure to real-world chemical mixtures and, eventually, to combined chemical and non-chemical stressors. These data and predictive models will inform risk management and remediation decisions. We will also be able to work collaboratively with risk reduction efforts, for example by conducting experimental toxicological assays, testing before and after mixtures to ensure that the proposed remedial actions reduce toxicity and that no unintended consequences are resulting in increased toxicity.

Outputs from Projects related to this task

(1) Draft method to predict chemical mixtures effects based on Adverse Outcome Pathways, FY15Q4.
(2)Methods for prioritizing chemical mixtures based on likelihood of adverse health outcome FY16,Q4.

Expected Products

(1) Draft methods to predict chemical mixtures effects based on Adverse Outcome Pathways Information from ToxCast high-throughput screening assays.

Type: OTHER Delivery Date (FY): 2015

(5) Dose response data for individual chemicals and mixtures with methods and models for analysis of mixture data based on consideration of the most appropriate computational model.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2014

(3) Data and models for assessing consistency with dose addition for mixtures of chemicals, with consideration of mixture composition on toxicity and additivity.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2016

(4) New data, methods and approaches for assessing the hazard of chemical mixtures and combined chemical and nonchemical stressors; integration of occurrence, exposure and toxicity data to priortize mixtures and cumulative exposures.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2016

(2) Computational Method to utilize chemicals' similarities in kinetics and dynamic (response) determinants to optimize clustering and interactions of clusters of chemicals within complex mixtures.

Type: DATA
SOFTWARE Delivery Date (FY): 2013

(6) Integrated screening level tool to determine the need to do a CRA, and tiered tools for applying

improved exposure and effects data for cumulative assessments of high priority chemicals, and improved risk management tools to address cumulative risks

Type: OTHER Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** No

Could NCER contribute to this task? No

Internal Collaborators (known or proposed)

NHEERL: David Herr, Hisham El-Masri and various technical staff NERL: Kent Thomas NCEA: TBD Other Internal Collaborators: OCSPP: TBD

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Research Strategy Developed	Scheduled: Q2 - 2012 Completed:
(Product 1) Identification of AOPs and HTS assays linked to them	Scheduled: Q2 - 2013 Completed:
(Product 1) Identify chemicals positive in HTS assays for identified AOPs	Scheduled: Q4 - 2013 Completed:
(Product 1) Literature search completed for mixtures studies with the identified chemicals	Scheduled: Q2 - 2014 Completed:
(Product 1) Draft Standard methodology	Scheduled: Q4 - 2015 Completed:
(Product 2) Identification of critical kinetic (e.g., partition coefficients, metabolism) and/or dynamic (e.g. common AOPs) proprieties for clustering chemicals in complex mixtures	Scheduled: Q1 - 2013 Completed:
(Product 2) Development of Methods to group chemicals within complex mixtures based on critical properties	Scheduled: Q3 - 2013 Completed:
(Product 2) Validation of developed methods against data generated from complex mixtures using cumulative risks tasks in CSS and other research programs (ACE or SSWR)	Scheduled: Q4 - 2013 Completed:
(Product 3) QA documentation approved	Scheduled: Q2 - 2012 Completed:
(Product 3) Evaluation of impact of dose expression on additivity evaluation	Scheduled: Q3 - 2013 Completed:
(Product 3) impact of mixing ratio on additivity evaluations	Scheduled: Q4

	- 2013 Completed:
(Product 3) Comparison of additivity evaluations based on external and internal dose	Scheduled: Q4 - 2014 Completed:
(Product 3) An understanding of the influence of non-additivity in one target organ on severity of toxicity in another target organ	Scheduled: Q4 - 2015 Completed:
(Product 3) Summary of factors that influence the ability to detect nonadditivity	Scheduled: Q4 - 2016 Completed:
(Product 4) QA documentation approved	Scheduled: Q2 - 2012 Completed:
(Product 4) methodologies for grouping contaminants	Scheduled: Q1 - 2014 Completed:
(Product 4) Evaluation of additivity methodologies	Scheduled: Q4 - 2014 Completed:
(Product 4) Impact of diabetes on mixtures toxicity	Scheduled: Q4 - 2015 Completed:
(Product 4) Methodology for integration of occurrence, exposure grouping methods and toxicity data to prioritize mixtures	Scheduled: Q4 - 2016 Completed:
(Product 5) Method for dose addition that incorporates consideration of the most appropriate model of the single chemical data	Scheduled: Q1 - 2013 Completed:
(Product 5) Report describing application of the developed method	Scheduled: Q3 - 2013 Completed:
(Product 5) Report describing the impact of the additivity model on outcome	Scheduled: Q4 - 2014 Completed:
(Product 6) Research plan to develop integrated screening and tiered tools for cumulative risk assessment and risk management, prepared in collaboration with HHRA and interested Program Offices and Regions".	Scheduled: Q4 - 2014 Completed:

Division Approved Yes

CSS

Prediction Tools, Models and Approaches to Inform Risk Management Actions and to Incorporate Sustainable Development

CSS 413

413

Carolyn Acheson
NRMRL
LRPCD

Topic/Theme

4 Cumulative Risk

Project

4.1 Developing, Refining, and Evaluating Data, Methods, Models, and Approaches across the Source-to-Outcome Continuum for Cumulative Risk Assessment/Management

Associated Project

None

Task Description

Risk management actions may alter the environmental impact of a stressor mixture throughout the source-to-outcome continuum. Innovative production methods and formulations may reduce resource needs, energy requirements, reliance on toxic reactants or catalysts, human and environmental toxicity, or may add value by reducing liability and improving product performance or acceptance. Similarly, improved risk mitigation and remedial actions may reduce resource and energy requirements, reduce volume and impact of residual streams, and enhance performance and societal acceptance. Sustainable development may affect the products commercially available, the manner in which they are used, societal norms, and thus, may have a varied effect on cumulative risk scenarios. As we move to a cumulative risk assessment approach that frames the assessment based on risk management options, all these types of risk management actions may be considered in evaluating options to ameliorate situations of unacceptable cumulative risk (National Academy of Sciences, 2009). The risk management actions considered will affect the speed and quality of information needs for Agency decision-making processes. Improved risk management technologies, tools, and approaches will provide EPA risk assessors with more options to ameliorate situations of unacceptable cumulative risk and allow EPA risk assessors to more quickly identify needed information, and in some cases, reduce information needs for cumulative risk assessments.

Rationale and Research Approach

Currently, the highest priority cumulative risk questions for which risk management information is needed involve wastewater treatment (WWT) and solid waste management. Our modern society and economy rely on these systems to handle their waste streams. Many questions exist about whether current technologies can adequately manage new concerns such as trace chemicals (TCs), particularly those with high biological activity. Modern wastewater treatment was designed to alleviate clean water problems by reducing pathogens, biological oxygen demand, and nitrogen levels in wastewater effluent. These treatment systems were not designed to remove chemicals present at low concentrations, and there is considerable uncertainty regarding the fate and transport of these chemicals. In addition, mixtures of these low level chemicals, or their degradates, may produce unforeseen consequences. The proposed research will include traditional wastewater research to manage these trace chemicals (such as evaluating existing and innovative treatment technologies, fate and transport following effluent discharge or biosolids land application), but will importantly move to innovative endpoints that combine analytical chemistry, bioinformatics, toxicology, and mode-of-action biological assays to provide a weight of evidence in decision-making for managing risk of wastewater (including emerging contaminants along with currently regulated parameters). Future solid waste research will characterize the fate and transformation of trace organic chemicals and other high priority chemicals in landfill environments. Using the innovative endpoints, future research will focus on providing a scientific basis for EPAs decisions as to whether additional regulation is merited, and whether current practices are effective. Specifically, lab and field studies are needed to resolve

uncertainties in degradation rates and establish persistence and fate of TCs (and pathogens in collaboration with SSWR). WWT operations (centralized plant, decentralized WWT processes, and sludge processing) and variables associated with land application (including sludge processing operations, application rate, application technique and agricultural practices, soil properties, and weather) affect the concentrations, fate, and transport of TCs. The current TCs of concern include: endocrine disrupting compounds (EDCs) such as steroid hormones and alkyl phenol ethoxylates (APEs); perfluorinated chemicals such as PFOA; nanomaterials; selected antibiotics and pharmaceuticals; and metals. Non-chemical stressors include: biological oxygen demand, microbes (fecal coliforms, E.coli, Salmonella); viruses (enteric, coliphage); and pathogens. This list will be expanded, or contracted, based on the availability of analytical methods in WWT matrices and resources. This research will be leveraged with the pathogen and water quality focused research on wastewater in SSWR (Task 2.1.e and 2.2.a).

Outputs from Projects related to this task

(1) Evaluation of selected PFCs and Pharmaceutical compounds in municipal solid waste landfills (2) A reduced list of "indicator chemicals" for routine monitoring of emerging contaminants in wastewater and receiving waters in support of regulatory policy for limits of discharge (3) Final data on the fate and transport of emerging chemicals of interest following land application of biosolids (4) Weight of evidence approach using "indicator chemicals" and selected MOA based bioassays to assess the efficacy of risk management of emerging contaminants in wastewater and receiving waters (5) Evaluation of selected compounds in municipal solid waste landfills (6) Data on the fate and transport of emerging chemicals of interest following land application of biosolids for mixtures identified in CSS cumulative risk research.

Expected Products

(1) Methods and approaches for evaluating the fate and transport of mixtures of emerging contaminants and selected modes of action in wastewater treatment in support of TSCA rule making.

Type: OTHER Delivery Date (FY): 2013

(3) Pretreatment options for concentrated discharges to wastewater collection systems and the economic benefits of pretreatment versus direct discharge to support pretreatment rule making

Type: OTHER Delivery Date (FY): 2015

(5) Interactions of emerging and traditional contaminants, modes of action responses traditional contaminants, pathogens, and microbial communities during wastewater treatment identified in CSS cumulative risk research

Type: OTHER Delivery Date (FY): 2015

(6) Data gap analysis on presence, fate and transport of selected compounds in the municipal solid waste stream.

Type: OTHER Delivery Date (FY): 2014

(7) Method for the evaluation of selected in municipal solid waste landfills.

Type: OTHER Delivery Date (FY): 2015

(9) Evaluation of selected in municipal solid waste compost.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2016

(10) Preliminary data on the fate and transport of emerging chemicals of interest following land application of biosolids in support of TSCA rule making.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(2) A reduced list of "indicator chemicals" for routine monitoring of emerging contaminants in wastewater and receiving waters in support of regulatory policy for limits of discharge

Type: OTHER

Delivery Date (FY): 2014

(4) Weight of evidence approach using "indicator chemicals" and selected MOA based bioassays to assess the efficacy of risk management of emerging contaminants in wastewater and receiving waters

Type: OTHER

Delivery Date (FY): 2015

(8) Evaluation of selected PFCs and Pharmaceutical compounds in municipal solid waste landfills.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(11) Final data on the fate and transport of emerging chemicals of interest following land application of biosolids

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2016

(12) Data on the interactions of emerging chemicals of interest, traditional contaminants, pathogens, and microbial communities following land application of biosolids

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2016

(13) Data on the fate and transport of emerging chemicals of interest following land application of biosolids for mixtures identified in CSS cumulative risk research

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2016

(14) Data on the interactions of emerging chemicals of interest, traditional contaminants, pathogens, and microbial communities following land application of biosolids for mixtures identified in CSS cumulative risk research

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2016

Start Date Q1 2012

End Date Q4 2016

Cross Research Project Output Supported?
Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

Potential team members include the following:
NRMRL: Marc Mills, Thabet Tolaymat

External Collaborators (known or proposed)

TBD

Milestones
None
Division Approved Yes

CSS Science, Approaches, Tools and Data for Informing Agency Chemical Registration Decisions

CSS 421

421

Kent Thomas
NERL
HEASD

Topic/Theme

4 Cumulative Risk

Project

4.2 Application, Translation, and Transfer of ORD Science, Data, Tools, Models, and Approaches for Selected Agency Risk Assessment/Management activities

Associated Project

None

Task Description

This task describes collaborative research efforts to use and evaluate data, methods, and models to support the Office of Chemical Safety and Pollution Prevention (OCSPP), Regions, and NCEA in their chemical assessment and registration activities. This task will employ scientific knowledge and results for informing Agency chemical risk assessment and registration decisions. Included in this task is the on-going translation and transfer of information needed to directly support specific Agency aggregate exposure and aggregate/cumulative risk assessment and risk management activities. High priority collaboration, research, and evaluation for our Agency partners will be completed under this task.

Rationale and Research Approach

Agency risk assessors and risk managers need evaluated science and data for decision-making. The Office of Chemical Safety and Pollution Prevention (OCSPP) serves as the primary EPA office reviewing and approving industry requests for the manufacture, distribution, and use of chemicals (including pesticides) as outlined in the Toxic Substances Control Act, Federal Insecticide, Fungicide, Rodenticide Act, and the Federal Food, Drug and Cosmetic Act. OCSPP routinely needs additional science and/or data to reassess registration decisions, industry provided data, or add to the weight of evidence for a specific decision. The Human Health Risk Assessment program will need additional science for IRIS reassessments. Regional risk managers need additional data to develop and evaluate risk reduction/mitigation strategies. All the Program and Regional offices routinely need data to respond to an external group's review of a pending EPA decision or an existing regulatory action. When these scientific issues arise, EPA Program Offices and Regions routinely request responsive ORD research to provide the additional science and/or data to inform the Agencys decision. Collaborative research will be conducted using evaluated science, methods, models, and tools to generate scientific data and understanding for supporting Program Office and/or Regional identified need(s). This research will be identified, prioritized, and conducted in collaborations with the Program Offices/Regions and may support the regulatory activities for a single chemical, a class of chemicals, or a relevant mixture of chemicals. Research activities anticipated (but not limited to) include: analysis of data using revised/enhanced models and/or informatic tools; evaluation of one or more groups of chemicals for key physical, chemical and/or toxicological attributes; characterization of degradation and/or metabolism pathways; generation and/or evaluation of epidemiological data; collection of limited laboratory or field data; and/or evaluation of a risk reduction method/approach. The initial focus will be providing exposure science collaboration/technical support to the inter-Agency Agricultural Health Study (AHS) and the Office of Pesticide Programs. The AHS is an ongoing, long-term, prospective epidemiological investigation of agricultural pesticide use and health in Iowa and North Carolina. The research is led by NCI and NIEHS, with collaborations and contributions from the U.S. EPA and NIOSH. ORD will provide scientific research staff collaboration to the inter-Agency AHS Executive Committee and the inter-Agency AHS Exposure Workgroup. The collaboration will contribute to the research design, implementation, and results publication and dissemination of AHS

data and results. ORD will collaborate with inter-Agency AHS efforts to improve occupational exposure assessment methods and applications for agricultural pesticide epidemiology, generate and evaluate biomonitoring data, and to examine exposure/outcome relationships. ORD collaboration with OPP will contribute to efforts to examine, understand, and use exposure and health outcome data from pesticide epidemiology, including and especially from the AHS, in risk assessment, pesticide review, and registration/re-registration decision-making. While the initial work focuses on human exposure to agricultural pesticides, the future research/support in this task will consider all human and ecological exposures to chemicals. It is anticipated that additional short-term ORD research collaborations with OCSPP, other Program Offices, and Regions will be included in the future under this task as specific needs are identified with regard to scientific knowledge for single- and multiple-chemical chemical registration and risk assessment activities.

Outputs from Projects related to this task

Through inter- and intra-Agency science collaborations, the Agricultural Health Study will continue to produce valuable and high-quality occupational agricultural pesticide exposure and health-outcome epidemiology results suitable for Agency consideration in pesticide risk assessment, review, and/or registration decision-making.

Expected Products

(1) Collaboration with the Agricultural Health Study inter-agency executive committee and exposure workgroup; and exposure research collaboration to improve and support the value of AHS pesticide epidemiological results.

Type: OTHER Delivery Date (FY): 2012

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** No

Could NCER contribute to this task? No

Internal Collaborators (known or proposed)	External Collaborators (known or proposed)
Office of Pesticide Programs; particularly with the Health Effects Division.	TBD

Milestones

ORD research collaboration on AHS inter-Agency Executive Committee and inter-Agency Exposure workgroup maintained	Scheduled: Q4 - 2012 Completed:
ORD collaborates with OPP on completion of OPPs exposure approach comparison white paper	Scheduled: Q4 - 2012 Completed:
ORD collaborates with AHS to provide an imputation approach for missing pesticide use information needed to improve power of epidemiological exposure-outcome analyses using AHS Phase II data	Scheduled: Q4 - 2012 Completed:
ORD collaborates with AHS on an epidemiological exposure-outcome cancer analysis for 2,4-D	Scheduled: Q4 - 2012 Completed:
ORD collaborates with AHS on an analysis of cumulative organophosphate pesticide use and patterns of use	Scheduled: Q4 - 2012 Completed:
ORD collaborates with AHS and OPP on molecular indicator/biomarker sub-study	Scheduled: Q4

(provided sufficient resources are available to complete sub-study, FY14) - 2014

Completed:

Division Approved Yes

CSS

Science, Approaches, Tools and Data for Informing Cumulative Risk Assessment and Risk Management for High Priority Classes/Groups of Chemicals

CSS 422

422

Chris Lau
NHEERL
TAD

Topic/Theme

4 Cumulative Risk

Project

4.2 Application, Translation, and Transfer of ORD Science, Data, Tools, Models, and Approaches for Selected Agency Risk Assessment/Management activities

Associated Project

None

Task Description

This task is focused on providing the Agency risk assessors and managers with specific data and scientific understanding on a number of high-priority chemicals and chemical mixtures, as well as unique risk assessment issues that have been identified by the program offices (OCSPP, OW). Research activities in this task are diverse and complementary, which entail characterization of source, fate and transport of chemicals, exposure pathway characterization, exposures and resulting dose estimation; dose-response evaluation of the adverse effects of single chemicals and their mixtures; computational modeling and measurement of chemical emission in the real world; cumulative hazard assessment based on high-throughput and high content systems biology data; and performance of risk management strategies, as well as the investigation of consumer behaviors that influence their chemical exposure. The outcomes of this research will provide immediate and medium-term support to the program offices for their rule-making decisions.

Rationale and Research Approach

To support the Agencys risk assessment and management efforts, this research will focus on a set of high priority chemicals identified by OCSPP and OW. These include, but are not limited to: fluorotelomer products (FTPs) and perfluorinated chemicals (PFCs); polychlorinated biphenyls (PCBs); dioxins and dioxin-like chemicals; formaldehyde; androgen disruptors; and spray polyurethane foams (SPF). PFCs are synthetic chemicals often used in the formulation of FTPs, and found pervasive in all environmental media (air, water, soil and food), measured in humans and wildlife, with research showing potential adverse effects in laboratory animals. OCSPP is pursuing regulatory actions on these chemicals under TSCA; OW is issuing Health Advisories; and OSWER has issued soil screening levels. In the environment, 14 PFCs have been routinely monitored, and risk assessment of these chemicals and products must take into consideration their mixtures/cumulative effects. Our research approaches entail four studies focusing on human exposure and one on adverse effects in laboratory animal models. Source identification of PFCs and their degradation in the environment have been major concerns of the program offices. Our research will focus on three environmental systems: fresh water, waste water treatment and soils. Sensitive analytical methods will be developed to determine PFC levels in surface and drinking water of various sources. Model systems such as semi-continuous activated sludge reactors will be used to determine the fate and transformation of PFCs, and PFC products will be evaluated for transformation by dosing soil microcosms (the last two measures will be monitored as function of time). Human exposure to PFCs will be assessed in two studies: (1) market monitoring research has been collecting consumer articles from the open market over a three-year span and PFC levels in these products are being determined, the market trends and potential reduction of PFCs upon chemical elimination efforts taken by manufacturers will be assessed; and (2) novel approaches and techniques will be developed for non-invasive human biomonitoring of PFC exposure, to promote population-based studies that include all ages (children in particular). In addition, the extent of fish consumption as a route of human exposure to PFCs will be

evaluated, as these chemicals are known to bioaccumulate in invertebrates and fish. Health effects study of PFCs involves four specific aims: evaluation of chemical toxicity at low doses to approximate human exposure scenarios; use of toxicogenomic approaches to identify modes of action for various PFCs, to reduce uncertainties associated with extrapolation of animal data to humans; in vitro studies to compare relative potencies of all 14 PFCs; and mixture studies using computational modeling and in vitro/in vivo confirmation to address cumulative risks of these chemicals. Adverse health effects from non-occupational exposure to PCBs have long been an Agency concern, especially childrens PCBs exposures. Caulk containing PCBs was used indoors and outdoors at some school buildings during the 1950s -1970s. Other PCB sources such as fluorescent light ballast capacitors, may also contribute to indoor PCB contamination. Considerable uncertainties remain regarding the extent to which children and staff members may be exposed to PCBs in schools. Two studies in this task will focus on PCBs in schools to better understand and characterize the sources, potential exposures, and generate the science and data to improve Agency risk management decisions. In the first study, relationships between PCB sources, environmental levels, and potential exposures will be investigated using building measurements. PCB source emissions and transport will also be evaluated using laboratory chamber testing. Indoor modeling approaches will be applied to describe emissions and transport, and SHEDS modeling is being used to estimate exposures and doses and to identify the important exposure pathways. In the second study, mitigation efforts will be devoted to evaluate the effectiveness of an encapsulation method that reduces the PCBs exposure by creating a barrier over the sources, and a PCB destruction method based on chemical reactions to remove PCBs by reducing PCBs to biphenyl. Results of this research will provide guidance to the program offices and regions for the development and implementation of long-term risk management solutions for old school buildings. The Agency is actively reviewing the health risk potentials of formaldehyde, establishing processes for testing, certification, and labeling of pressed-wood materials and finished goods required by the Formaldehyde Standards for Composite Wood Products Act, and conducting Registration Review of antimicrobial biocides that release formaldehyde. These activities require a clear understanding of all indoor sources of formaldehyde and factors that affect its fate and transport. Research in this task will focus on characterization of formaldehyde source emissions from building materials and consumer products. It will develop novel tools, methods and models to evaluate formaldehyde source emissions for risk assessment and risk management, in order to support the Agencys formaldehyde regulation and biocide registration. Due to the increasing use of SPF insulation and the proliferation of consumer products formulated with SPF reagents that are known respiratory irritants, EPA has a critical need to understand the multi-pollutant emissions from these products as the basis for improved risk management. Studies in this task will produce methods, data, and models that characterize emissions from SPF during application, curing, and post-curing across a range of environmental conditions, and link source, exposure to potential adverse health effects (using mechanistic mouse models of allergic immune hypersensitivity via the dermal and respiratory exposure routes to investigate relationships between SPF emissions, immune sensitization, and genetic susceptibility factors). These data will be invaluable for EPA (OPPT, Energy Star, Indoor Environments, Green Building Programs), CPSC, OSHA, ATSDR, and NIOSH for evaluating adequacy of existing regulatory approaches, and for EPA Regional Offices in informing and assisting State and local Commerce, Energy, Environment and Health programs involved in educating and informing the public in exposure control, chemical management and energy efficiency/demand reduction options and technologies. The Agency needs to develop methods and expertise to incorporate molecular and systems biology data into risk assessments. Two studies in this task, part of the interagency Advancing the Next Generation of Risk Assessment Program, will address these needs by utilizing the full spectrum of molecular systems biology data, including high throughput (HTP) screening assays. Testicular dysgenesis is chosen for modeling because there is a wealth of HTP (ToxCast), toxicogenomic, and traditional toxicological data. Single chemicals (e.g. phthalates) and cumulative exposure data for agents that cause testicular dysgenesis will be examined. In addition, the mixture effects (additivity or synergism) of dioxins and dioxin-like chemicals will be examined. A prototype hazard and dose-response assessment will be derived, with particular focus on molecular systems biology data. We will examine how to utilize these data within a risk assessment, and how to integrate the knowledge from these data together to make informed assessments of the entire body of the science. This information will support the IRIS, Provisional Peer Reviewed Toxicology Value (PPRTV), and Integrated Science Assessment (ISA) programs. STAR extramural research will provide complementary science on how consumer choice

and use influence human chemical exposure. Risk assessors will be able to use this information to develop risk assessments that go beyond standard assumptions about diet, age, occupation, and daily travel to include additional factors that influence chemical exposure. Examples might include why consumers choose pesticides over nonchemical insect control methods, or why they deploy scent-releasing products rather than cleaning up mold and mildew. Research may examine behavioral differences between socioeconomic groups or regions and other factors such as the influence of friends or other admired persons on individual choices.

Outputs from Projects related to this task

(1) Characterization of development toxicity of PFOA at low-dose exposure (NHEERL) (2) Evaluation of comparative potency of PFCs by in vitro models (NHEERL) (3) Evaluation of PFC mixture effects by in vitro and in vivo models (NHEERL) (4) Data for characterizing the transformation and fate of fluorotelomer products in wastewater treatment processes (NRMRL) (5) Data for characterizing the transformation and fate of fluorotelomer products in soils (NERL) (6) Market trend monitoring for PFCAs in consumer articles (NRMRL) (7) Market trend monitoring for PFCA precursors in consumer articles (NRMRL) (8) Data and model results for PCBs in schools to provide information needed to develop improved and cost-effective mitigation and remediation approaches (NERL) (9) Evaluation of PCB encapsulants (NRMRL) (10) Evaluation of the relationship between PFC levels in freshwater resources and resident fish populations (NRMRL) (11) Formaldehyde reference material to support OPPT's rulemaking for the formaldehyde act and the third party certification program (NRMRL) (12) Source emission data to OPP for biocides registration process (formaldehyde-releasers in products) (NRMRL) (13) Formaldehyde Henrys Law constants in water solution with/without surfactants (NRMRL) (14) Test methods to characterize the emissions from SPF products (NRMRL) (15) Emissions data for aldehydes, amines, isocyanates, and flame retardants from SPF products (NRMRL) (16) Parameters for source emissions models to relate emissions to potential exposures indoors (NRMRL) (17) Demonstrated in vivo immunotoxicological methods for the hazard identification and risk assessment/dose-assessment of SPF vapor phase emissions characterization experiments (non-commitment) (NHEERL) (18) Conceptual mode of action framework for suspected disease pathways, including a database describing key end-points associated with SPF exposure (NHEERL) (19) Data and assessment of comparative risk of dermal and inhalation exposure pathways through a data-base of functional, cellular, genomic and proteomic end-points. (NHEERL) (20) Next Generation Risk Assessment prototypes of hazard and dose-response assessments for dioxin and dioxin-like chemicals, and for the cumulative testicular dysgenesis effect (NCEA) (21) Guidance for HHRA on incorporating molecular and systems biology data into IRIS, PPRTV and ISAs (NCEA).

Expected Products

(13) Data and tools for formaldehyde source emission testing and modeling.

Type: DATA
DATABASE

Delivery Date (FY): 2016

(12) Extramural research (STAR grant) on consumer behaviors that influence consumer product use and resulting chemical exposure.

Type: EXTRAMURAL DOCUMENT
GRANT

Delivery Date (FY): 2016

(2) Data and methods for characterizing the degradation of fluorotelomer polymers in soils (NERL).

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(3) Data and methods for characterizing the degradation of fluorotelomer polymers from wastewater treatment processes (NRMRL).

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(4) Market monitoring data for PFCs and precursors in consumer articles.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2012

(5) Methods and data for characterizing human PFC exposure from multiple routes and pathways.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2012

(6) Methods and data for characterizing occurrence and variability of PFC mixtures in freshwater sources.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2012

(9) Test method and data for characterizing the emissions from spray foam (SPF) consumer products.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(10) Androgen disruption (e.g., testicular dysgenesis syndrome, androgen activity disruption): Individual chemical and cumulative hazard assessments using computational, high throughput (ToxCast) and high content systems biology data (triazines, phthalates).

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2012

(11) Dioxins and dioxin-like chemicals: Individual chemical and cumulative risk using hazard assessments using computational, high throughput (ToxCast) and high content systems biology data.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(1) Toxicity data to reduce the uncertainty in the PFOA risk assessment and for comparing the potency of individual and mixtures of other important PFCs.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(7) Data, methods, and models for characterizing sources from, and exposures to, PCBs in school environments.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2012

(8) Data, methods, and techniques for mitigating PCB sources in school environments.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2012

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NHEERL: B Abbott, K Das, C Wolf, A Watkins, J Andrews (TAD), M Rosen (ISTD), M Williams, R Luebke (EHPD) NERL: A Lindstrom, M Strynar, J Washington, K Thomas, J Xue NRMRL: C Acheson, M Mills, D Timberlake, L Staley, Z Guo, X Liu, M Mason NCEA: L Burgoon NCER: A Sergeant

External Collaborators (known or proposed)

TBD

Milestones

None

Division Approved Yes

CSS Assessment and Mitigation Case Studies of Targeted Chemicals and Products to Identify Areas to Incorporate Sustainability

CSS 512 512

Diana Bless
NRMRL
STD

Topic/Theme

5 Life Cycle Considerations

Project

5.1 Risk Management for Sustainability

Associated Project

None

Task Description

This task is focused on the incorporation of sustainability into Agency decision making. To increase the efficiency and effectiveness of ORD support, it is important to form partnerships with EPA Program and Regional Offices to conduct robust sustainability assessment case studies regarding the life cycle of targeted chemicals, compounds, processes, and products to identify what sustainability means for the various parts of EPA. The duration of the case studies will range from one to five years, based on the properties of the chemicals and products themselves, as well as the complexities of their production, use, reuse and disposal. The case studies will address the more challenging issues facing EPA when managing emerging chemicals and materials of concern (i.e., nanoproducts, E-waste and rare earth metals, EDCs, etc.) while serving as a starting point to build a risk management strategy within the Agency to inform the development of sustainable solutions to prevent, mitigate or remediate the associated risks. The data sets generated by the case studies will be useful in the development/validation of predictive models for the fate and transport of similar chemicals and products in the environment. In addition, a comparison of the case studies will highlight any unique needs of the Program Offices and Regions that must be considered when framing the holistic approach to risk management for sustainability. The output from this task will contribute to a collaborative risk management strategy that unifies the incorporation of sustainability within the EPA.

Rationale and Research Approach

The incorporation of sustainability into decision making for the EPA is not a trivial pursuit. There are many questions that must be answered regarding the proper context of sustainability within the mandates given to EPA by congress. Furthermore, risk management for sustainability will vary from Program Office (PO) to Program Office and Region to Region. ORD can help the POs and Regions address these issues and arrive at a solution that is consistent across the various entities of EPA. This research will be accomplished using various case studies that allow ORD to work with specific POs and/or Regions to incorporate sustainability concepts into their risk management strategies while addressing their immediate needs. The knowledge from this work will help posture ORD to better support the future needs of the POs and Regions. To begin, this task will involve the four case studies described below. Case Study 1 (OCSPP). It is important to understand the challenges associated with the implementation of LCA methods for nanotechnology to successfully develop a guidance framework for risk management of nanoproducts that promotes sustainability. These challenges include constructing life cycle inventories (LCIs) for emerging nanoproducts, developing models to predict the behavior of nanomaterials released throughout the product life cycle, and verifying the applicability of current impact assessment methodologies for nanoproducts. The first part of this case study will focus on the assembly of a complete LCI for specified silver-based and carbon nanotube nanoproducts (i.e., nano-enabled textiles, composite plastics, etc.) with emphasis on compiling primary (manufacturer-supplied) data for the manufacturing phase and developing new methods to quickly simulate use and disposal of the nanoproducts to fill data gaps in these stages. The second part of this study will determine and evaluate the characteristic retention and breakthrough of target nanomaterials (Ag, CNTs, TiO2) through a porous media under various reaction environments (pH, redox conditions, etc)

and in the presence/absence of encapsulating agent such as cellulose, humic and fulvic acids, cations and anions, etc. The final part of this study will involve a multi-disciplinary team consisting of toxicologists, environmental engineers, chemists, chemical engineers and LCA practitioners that will take current nanotechnology data being generated within ORD (including this task) and determine how to best apply it in an LCA context using TRACI (the Tool for the Reduction and Assessment of Chemical and other environmental Impacts), the EPA-developed impact assessment tool. Case Study 2 (E-waste Initiative, Region 8). Rare earth elements (REEs) are a group of specialty metals with unique physical, chemical and light emitting properties that are seeing dramatic increase in demand, owing to their technological applications. Currently, the U.S. imports 100 percent of its REEs from other countries, with roughly 95 percent coming from China, according to the U.S. Geological Survey. Little if anything is known about their acquisition, manufacture, use and fate, and end-of-life phase especially for electronics. A life cycle perspective will be taken towards understanding the flow and environmental impact of rare earth elements (REEs) in their acquisition, manufacture, use, recycling, and endoflife phase for electronics. The target elements or chemicals will be identified based on criteria such as their occurrence in electronic products, relative toxicity, and magnitude of environmental release, occupational release during manufacture, recycling, and endoflife and global scarcity of resources. To help identify target compounds, a workshop to discuss E-waste and how sustainability can be used to improve the performance of the electronics industry will conducted by the EPA. Upon identification of a target element or chemical, a two tier approach will be taken to identify and quantify the environmental impacts associated with an REE. The first tier will be a life cycle assessment of the element/chemical from acquisition to manufacture for both the REE and the supporting plastics needed to manufacture the product. The second tier will be an assessment from use to end-of-use for that element/chemical, which includes fate in multiple media and product lifetime, exposure, product substitution, and disposal/recycling methods. The project proposes to do sampling at collaborative recycling facility in RTP (GEEP, Inc.) and within our laboratory to understand materials flow in recycling processes. Case Study 3 (OGWDW). Numerous organic contaminants of emerging concern (CECs), including endocrine disrupting compounds (EDCs), pharmaceuticals, personal care products, pesticides, algal products, etc. have been detected in the environment. The presence of these contaminants has led to concerns over the potential human and ecological health risks that may be associated with these contaminants, such as reproductive impairment, increased incidences of cancer, and development of antibiotic-resistant bacteria. Many of the compounds which have been detected to date are present in the aqueous environment, resulting primarily from their introduction from domestic and industrial sewage treatment systems and wet-weather runoff. The Office of Ground Water and Drinking Water (OGWDW) has included several estrogens (EDCs) on the current Chemical Contaminant List (CCL) due to their presence in surface waters and their documented health effects. Information on the identity, concentration, transport, fate and potential transformation/degradation of these contaminants within the environment and following various water treatment processes is needed to conduct a holistic assessment of human and ecological exposures. This data is also needed to validate, improve and/or develop new exposure models. Although analytical methods exist for many of these compounds and their by-products, new and/or improved methods will be developed to facilitate the collection of data on selected CECs present in water matrices (e.g. surface waters, drinking waters). Surface waters impacted by wastewater treatment effluents (centralized and decentralized), agricultural wet-weather runoff, etc. will be will be sampled over time and evaluated for the presence of selected CECs. Additionally, the effectiveness of various water treatment processes (e.g. wastewater and drinking water treatment) to remove/transform/degrade the selected organic contaminants will be evaluated. Case Study 4 (Regions). The use of zero valent nanometals during groundwater remediation for chlorinated organics and heavy metals has received significant attention as a promising technology. Regional offices that monitor these sites have raised concerns regarding the life cycle implications of such treatments. The proposed research is expected to greatly improve the fundamental knowledge of these technologies by addressing key issues, including green nanoparticle synthesis, transport, retention, release and bioavailability nanomaterials, as well as their interaction with other ecosystems in natural porous media. The main objective of this research is to evaluate factors that control fate and transport of nanomaterials (zerovalent iron, iron oxides, zerovalent copper, CeO2, ZnO, zerovalent silver, titania, carbon nanotubes, etc). The factors include inherent properties of nanomaterials (size, shape, chemical composition, crystalinity, etc), characteristics of porous media (size and purity of sand, soil texture, organic matter content, metal oxide coatings, etc), and

geochemical parameters of water (pH, ionic strength, ion valance, natural organic matter, flow rate, time). The life cycle of nanomaterials use can be more accurately assessed once their fate and transport are fully understood. As part of this study, a field test of emulsified zero valent iron (EZVI) nanoparticles is ongoing to assess the treatment of chlorinated ethenes. This study will provide data to evaluate the long-term effectiveness and applicability of the EZVI technology for site remediation and to examine the fate and transport of injected nanoiron particles.

Outputs from Projects related to this task

Risk management strategy for sustainability

Expected Products

(6) Data collection and interpretation to document the occurrence, temporal variations, and potential transformations within the environment and following various water treatment processes of selected organic contaminants of emerging concern (CECs). Selection of CECs will be based on relevancy to the needs of the Office of Ground Water and Drinking Water (OGWDW) and results from studies currently in progress and recent reports in the literature.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(1) the following will be delivered: (i) a life cycle inventory (LCI) for a silver nanoproduct with documented data gaps and its demonstrated application in a life cycle assessment (LCA); (ii) a life cycle inventory for a CNT-composite product and its demonstrated use in LCA.

Type: OTHER

Delivery Date (FY): 2012

(2) EPA report to provide the following: (i) analysis of the current market for Rare Earth Elements (REEs) in electronics with identification of high priority materials and applications; (ii) data gap analysis of a potential LCI for a high priority product for prioritization of data gathering efforts; and (iii) preliminary analysis of the product stream from an electronics recycling facility for REE content to understand current end-of-life behavior.

Type: OTHER

Delivery Date (FY): 2014

(3)Documentation of methods will be provided to simulate the fate of nanomaterials (Ag, TiO2, CNTs) during consumer product use and predict their behavior in landfills using numerical modeling and experimental data.

Type: OTHER

Delivery Date (FY): 2014

(4) Documentation will be provided to evaluate green synthesis of surface-supported metallic and bimetallic systems as a viable option for use in the remediation of POPs.

Type: OTHER

Delivery Date (FY): 2014

(5) A complete LCI with identified data gaps for a high priority e-product with an accompanying EPA report describing sampling and mass balance closure for REE at a thermal recycling facility.

Type: OTHER

Delivery Date (FY): 2014

(7) Methods and models will be presented to predict the life-cycle fate of nanomaterials (Ag, TiO2, CNTs) in environmental vectors including fate and transport in porous media and sedimentation and aggregation of these nanomaterials as affected by nanomaterial properties.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(8) A developed protocol to generate a life cycle inventory for the holistic assessment of consumer

nanoproducts including collection of primary manufacturing data, simulation of use and disposal data, and prediction of the environmental fate and transport of any nanocomponent releases.

Type: OTHER Delivery Date (FY): 2015

(9) A complete methodology for life cycle impact assessment of nanomaterials (components and/or products) with all necessary characterization factors available in a format that is useable with EPA's TRACI in major LCA software applications (SimaPro, GaBi, OopenLCA, etc.).

Type: OTHER Delivery Date (FY): 2015

(10) Guidelines for the use of nanomaterials in remediation based on experimental evaluation of the impacts associated with reactive/supported mono and bi-metallic systems.

Type: OTHER Delivery Date (FY): 2016

(11) A workshop will be held to evaluate current trends in electronic manufacturing and identify opportunities to incorporate green principles for sustainability.

Type: OTHER Delivery Date (FY): 2012

(12) A life cycle inventory will be assembled and applied to a stream-lined LCA of plastics used in the manufacture of electronics.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2013

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?**

Could NCER contribute to this task?

Internal Collaborators (known or proposed)

Potential team members include the following: NRMRL: David E. Meyer, Souhail Al-Abed, Cissy Ma, Mary Ann Curran, Jane Bare, Michael Gonzalez, Brian Gullet, Jeff Ryan, Chunming Su, Kathleen Schenck, Endalkachew Sahle-Demessie and Subhas Sikdar .

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Completed Life Cycle Inventory for nanomanufacturing of nanoscale Silver and CNTs using industrial partners	Scheduled: Q2 - 2012 Completed:
(Product 1) Completed Life Cycle Inventory for entire product life cycle of both CNT and nanoscale Silver products	Scheduled: Q3 - 2012 Completed:
(Product 2) Analysis of on-site samples for REEs and development of sampling and QA plan	Scheduled: Q4 - 2012 Completed:
(Product 2) Complete review of State-of-the-Art technologies for Rare Earth Element mining and processing	Scheduled: Q3 - 2013

(Product 3) Complete studies on matrix-dependent fate and transport of nanomaterials in soil and sediments.	Completed: Scheduled: Q4 - 2012
(Product 3) Complete studies to predict nanomaterial behavior in landfills by means of numerical modeling and simulated field tests.	Completed: Scheduled: Q4 - 2013
(Product 4) EPA research brief on transformation of nanoiron in the subsurface	Completed: Scheduled: Q4 - 2012
(Product 4) Complete studies on TiO2 transport at low ionic strength	Completed: Scheduled: Q3 - 2012
(Product 4) Complete studies on TiO2 aggregation and sedimentation as affected by nanomaterial properties	Completed: Scheduled: Q4 - 2012
(Product 4) Complete studies on treatment of source zone chlorinated solvents using emulsified zerovalent iron	Completed: Scheduled: Q4 - 2013
(Product 4) Complete long-term monitoring of a field test using emulsified zerovalent iron for treatment of source zone DNAPL	Completed: Scheduled: Q4 - 2014
(Product 4) Complete studies on transport of nanocopper in porous media	Completed: Scheduled: Q4 - 2014
(Product 4) Complete studies on fate and transport of nanomaterials in saturated porous media	Completed: Scheduled: Q4 - 2014
(Product 5) Nomination of product and components for targeted recycling, product substitution, remanufacturing to minimize loss or maximize recovery of REE	Completed: Scheduled: Q4 - 2013
(Product 6) Validation of analytical methods completed, data collection in progress	Completed: Scheduled: Q4 - 2013
(Product 6) Report/manuscript on the occurrence and potential transformations of selected contaminants of emerging concern in surface waters and following various water treatment processes.	Completed: Scheduled: Q4 - 2014
(Product 9) Complete gap analysis for application of existing LCA impact models (i.e. USETOX, TRACI, etc.) to nanomaterials	Completed: Scheduled: Q3 - 2013
(Product 9) Complete model derivation for nanotechnology impact assessment.	Completed: Scheduled: Q4 - 2014
(Product 10) Complete studies on TiO2 transport in real groundwater	Completed: Scheduled: Q4 - 2015
(Product 10) Complete studies on CeO2 transport in porous media	Completed: Scheduled: Q4

	- 2016 Completed:
(Product 12) Overview report of literature review on the various plastics used to make electronic products.	Scheduled: Q2 - 2012 Completed:
(Product 12) A completed life cycle inventory with impact assessment using TRACI on a selected plastic used in the manufacture of an electronic product.	Scheduled: Q4 - 2012 Completed:
(Product 5) Product (2) is a milestone for this product.	Scheduled: Q4 - 2014 Completed:
(Product 7) Product (3) is a milestone for this product.	Scheduled: Q4 - 2014 Completed:
(Product 8) Product (3) is a milestone for this product.	Scheduled: Q4 - 2014 Completed:
(Product 8) Product (7) is a milestone for this product.	Scheduled: Q4 - 2015 Completed:
(Product 8) Product (1) is a milestone for this product.	Scheduled: Q3 - 2012 Completed:
(Product 9) Product (8) is a milestone for this product.	Scheduled: Q4 - 2015 Completed:
(Product 10) Product (4) is a milestone for this product.	Scheduled: Q4 - 2014 Completed:

Division Approved Yes

CSS

Integration of Federal Data Sources to Form Sustainability Data Network

CSS 511 511

David Meyer
NRMRL
STD

Topic/Theme

5 Life Cycle Considerations

Project

5.1 Risk Management for Sustainability

Associated Project

None

Task Description

This task will focus on the development of a data network to support risk management for sustainability within the Agency. Several projects within the CSS research action plan focus on centralizing specific types of data collected within the Agency (i.e., toxicology data, fate and transport data, etc.). The output from this task will further combine these efforts into a format that yields readily useable data to meet the assessment needs of the program offices and regions in a manner that is scientifically defensible when promoting sustainability. As an additional output, the efforts of this task can be used to help establish open communication and sharing across the federal agencies to expand the quantity and type of data that can be used for assessment while reducing redundancies in data generation/collection.

Rationale and Research Approach

The knowledge needed to implement decisions for sustainability will vary among Program Offices (POs) and Regions. The only way data sets can be created to meet these individual needs is to work with the POs and regions to determine how sustainability can be incorporated into their Agency functions and what data is necessary to provide adequate knowledge for such decision making. In this respect, ORD can provide guidance to the POs and Regions on what other factors may be included in the decision making process beyond those associated with the traditional risk paradigm. Therefore, this task will work in tandem with the case studies established in CSS Task 5.1.2 to solicit the needed input from the POs and Regions. The task will first involve work with OCSPP using the life cycle inventories (LCI) compiled for selected nanoproducts as a basis to begin development of a sustainability data set. The LCI will contain all information needed to perform a Life Cycle Assessment of such products and can be used to populate the database with representative environmental impact data. Decision making for sustainability will require more than knowledge of environmental impacts. The supporting research will examine what other data could be complimentary to the LCI data when rendering decisions for sustainability while regulating chemicals and processes. This may include a broad range of factors including toxicity, resource and material management, economic impact and market drivers, public perception, etc. Once these factors have been identified, the goal will be to determine what information ORD will need to generate internally and which factors could possibly be obtained from other Federal Agencies to reduce the resources needed for ORD research. After the initial work with OCSPP to establish a sustainability data set is completed, the task will begin to incorporate data from other case studies while soliciting the applicable PO or Region for input. For example, OW will be engaged in the process through work to detect and understand water contaminants such as endocrine disrupting compounds (EDCs), pharmaceuticals, personal care products, pesticides, algal products, etc. An examination of nano-based remediation can involve the Regions in the development process. A study of rare earth elements (REEs) and E-waste will require input from both POs and Regions. By using this variety of case studies, the resulting sustainability database will be reflective of the needs of the Agency and not specific to a particular PO or Region. The intent of this work is to help integrate the concept of sustainability into the Agency in a consistent manner.

Outputs from Projects related to this task

This work will provide a centralized data system that supplies the data (either raw or aggregated) necessary to implement specified assessment methodologies for risk management that addresses sustainability within the program offices and regions in a standardized format.

Expected Products

(1) Preliminary sustainability database design based on a model case of LCI generated for a nano-silver consumer product and developed in collaboration with OCSPP and in coordination with related CSS databases (either developed or proposed).

Type: DATA DATABASE | Delivery Date (FY): 2012

(2) Demonstration of data submission procedures for the centralized sustainability data base using LCI data generated for a high-priority E-product.

Type: OTHER | Delivery Date (FY): 2014

(4) Centralized Sustainability database for use with CSS dashboards and widgets that integrates databases and models generated across CSS (inherent properties, toxicity models, impact characterization factors, etc.) with external Federal data sources (for example USGS data on U.S. silver supplies, NIOSH data on workplace exposure to nanomaterials, etc.) to provide relevant Agency decision-makers (OCSPP, OW, Regions, etc.) with centralized access to data necessary to establish a life cycle inventory for chemicals, processes, and products to support sustainable decision making during risk management.

Type: DATA DATABASE | Delivery Date (FY): 2016

(3) Final sustainability database design expanded using both data describing the fate of selected organic contaminants of emerging concern (including, endocrine disrupting compounds (EDCs), pharmaceuticals, personal care products, pesticides, algal products, etc.) in water treatment processes and data related to use of nanomaterials in groundwater remediation applications.

Type: DATA DATABASE | Delivery Date (FY): 2015

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NRMRL: Souhail Al-Abed, Mary Ann Curran, Diana Bless, Brian Gullett, Kathy Schenck

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Provide OCSPP with a copy of a Life Cycle Inventory for nano Ag and initiate dialogue regarding additional parameters to include for a broader consideration of sustainability.	Scheduled: Q3 - 2012 Completed:
(Product 2) Complete design of data submission form to use for collection of REE LCI.	Scheduled: Q4 - 2013

(Product 3) Identify and initiate contact with appropriate Program Offices and Regions for remaining case studies	Completed: Scheduled: Q1 - 2014
(Product 4) Obtain final approval from all Program Offices and Regions regarding the type, quantity, and quality of data needed for the database.	Completed: Scheduled: Q4 - 2014
(Product 4) Establish database platform and coding requirements.	Completed: Scheduled: Q1 - 2015
	Completed:

Division Approved Yes

CSS

Advancing Green Engineering for Sustainable Chemical Processes

CSS 522 522

William Barrett
NRMRL
STD

Topic/Theme

5 Life Cycle Considerations

Project

5.2 Sustainable Approaches to Chemicals and Processes

Associated Project

None

Task Description

The twelve principles of Green Engineering can be used to significantly improve the sustainability of chemical processes and their resulting chemicals and products. By developing and advancing innovative solutions based on pollution prevention, the disciplines of engineering and chemistry can be merged. This task develops applications and methodologies for improving the sustainability of a production process. To achieve this, this task focuses on developing models, approaches and tools for innovative chemical reactor geometries, separation systems, and process simulation and modeling software developed in conjunction with Task 5.2.1.

Rationale and Research Approach

Separation processes account for ~15% of world energy consumption resulting in a significant quantity of energy-related pollutant emissions. In order to reduce the amount of energy used in these separation processes, three approaches can be considered: improve the performance of the reactor system by reducing solvent use and byproduct production, develop separation technologies that require less energy, and improve energy utilization in the process. This task focuses on the use of process modeling and material synthesis to improve the reaction and separation systems, using the first two options listed above. Reactor Modeling Traditional chemical reaction systems rely upon solvents to allow reacting molecules to move into their relative positions and collide to initiate a reaction. Often, the solvent/reactant system interaction and molecular configurations of the reactants result in the formation of unwanted by-products and the need for separation technologies. Designing reactor configurations to improve the mixing of reactants can lead to eliminating the need for solvents and a reduction in process energy requirements. The reactor system that will be modeled is a novel, rotating tube-in-tube geometry that has been demonstrated to produce chemicals in high yields, with low by-product formation, and minimal need for solvents. The need to model this system arises from needing to know energy requirements and to predict reaction conditions. The reactor models will consist of coupled partial differential equations (PDE) that describe the simultaneous heat and mass transport phenomenon occurring within the reactor. Solutions to these equations are obtained using computational techniques such as finite difference and finite element mathematics. Mathematical modeling of the reactor system will provide predictive models that will reduce the time required to design the overall process and provide a platform to quickly optimize the system without the need for extensive laboratory experimentation. The simulated system can then be used to assess the overall sustainability the process. Membrane Separation Development As stated above, separation processes account for a significant portion of the energy used in chemical production and solvent recovery for reuse. Membrane-based processes are useful for the separation of bio-based fuels from the water used in the fermentation process and for the purification of solvents for reuse. Membranes synthesized from a combination of zeolitic and polymeric materials have been demonstrated to effectively separate ethanol from water. Further, these membranes can be designed specifically to separate biobutanol from water. OTAQ (OAR) is interested on the potential of using biobutanol as a fuel substitute for bioethanol. Biobutanol potentially produces less greenhouse gas emissions when compared to bioethanol. This task will focus on the development of membrane technologies that have lower energy

utilization than traditional biofuel separation and solvent purification technologies (i.e. distillation). Membrane Separation Modeling Membrane separations occur, at the molecular level, due to interactions between the membrane materials and the chemicals being separated. The modeling of the membrane process at this level provides insight into how interactions between the membrane itself and the chemical being separated affect membrane system performance. This modeling can lead to tailoring various membrane materials to the separation system and improving the separation process. Through proper material selection, the energy required to separate two chemicals can be greatly reduced. This modeling effort will be used to predict the performance of the membrane system and will be verified against the membrane development portion this task. The ability to predict the performance of a membrane process from first principles, for a known system such as ethanol-water, will advance the ability to predictively model the performance of membranes for other separation operations and lead to a reduction of the energy requirements for these separation processes. Process Simulation Simulation models for the entire chemical process will be assembled and run from the reactor and membrane models developed in this task and described above. The process simulation model will then be used to optimize the overall manufacturing process and also utilizing the process sustainability indicators developed in Task 5.2.3. This provides a mechanism for applying the principles of Green Engineering in the manufacturing process and allows for sustainable manufacturing allowing OCSPP to prevent pollution before it is created. Applying green engineering principles to the above problems will provide insight into bridging the divide between the science occurring at the molecular level and the environmental problems associated with production at the local, state, regional, national and global level. Improvements in reactor and membrane technologies will result in the development and implementation of chemical processes with less energy intensive separation requirements. The models of the chemical processes developed in this task can be used as part of a model of the overall supply chain (linked to Tasks 5.2.1, 5.2.3, and 5.2.4) which can be used to understand environmental life cycle implications of the production process. This will serve OSCPPs goals of prevention instead of treatment, design for separation, maximizing efficiency, integrating material and energy flows, and design for commercial afterlife. Specifically, the experience obtained from this task can be used to foster future collaborations with OPPTs Chemical Engineering Branch (CEB) to address pertinent separation challenges. Potential applications will include solvent recovery in pharmaceutical applications and non-contact quenching. The knowledge developed in this task will be applicable to OPPT CEBs development of the Green Engineering textbook to help promote sustainable processes during chemical manufacturing.

Outputs from Projects related to this task

Innovative and comprehensive life cycle approaches for the design and evaluation of sustainable production and use of commodity and specialty chemicals.

Expected Products

(1) Documentation of the development of a finite element method (FEM) simulation model describing a case study of a spinning tube-in-tube reactor which can be used to develop innovative solutions for pollution prevention through sustainability.

Type: OTHER Delivery Date (FY): 2012

(4) Documentation describing the application of a continuous flow reactor model for process chemistry that demonstrates the ability to predict optimum reaction conditions for sustainable manufacturing as a means for OCSPP to prevent pollution before it happens.

Type: OTHER Delivery Date (FY): 2014

(3) Membrane for the green separation of ethanol from water using combinations of zeolitic and polymeric materials to assess biobutanol as a fuel substitute for bioethanol to potentially lessen greenhouse gas emissions.

Type: OTHER Delivery Date (FY): 2013

(2) Method for efficient green process design using reactor simulation.

Type: OTHER Delivery Date (FY): 2013

Start Date Q1 2012 **End Date** Q4 2014 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NRMRL: Ray Smith, David Meyer, Lee Vane, Paul Harten

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Complete model build and solution in COMSOL software for the synthesis of Folpan.	Scheduled: Q3 - 2012 Completed:
(Product 2) Obtain laboratory data from STT reactor group for Case Study 1 (TBD).	Scheduled: Q3 - 2012 Completed:
(Product 2) Complete model verification using Case study 1 (TBD).	Scheduled: Q4 - 2013 Completed:
(Product 3) Complete evaluation of mixed matrix membranes containing silicone and fluorosilicone rubbers and zeolites for the separation of ethanol-water mixtures.	Scheduled: Q3 - 2012 Completed:
(Product 3) Complete evaluation of commercial and pre-commercial membrane modules from CRADA partner for the removal of trace amounts of water from alcohol vapor as a less energy-intensive alternative to conventional technologies for the production of bioethanol and biobutanol.	Scheduled: Q4 - 2012 Completed:
(Product 3) Complete demonstration of integrated hybrid membrane-based separation system for ethanol- and butanol-containing fermentation broths.	Scheduled: Q4 - 2012 Completed:
(Product 3) Complete state-of-the-science analysis of membranes and membrane processes for the efficient recovery and purification of butanol-based biofuels.	Scheduled: Q4 - 2013 Completed:
(Product 3) Complete evaluation of a functionalized polymer membrane and combinations of functionalized polymer and zeolitic particles for the separation of ethanol-water and butanol-water mixtures.	Scheduled: Q4 - 2013 Completed:
(Product 4) Complete design of experimental synthesis conditions using simulation program for Case Study 2 (TBD)	Scheduled: Q4 - 2013 Completed:
(Product 4) Complete analysis of experimental results in comparison to simulated results for Case Study 2 (TBD) for model evaluation.	Scheduled: Q4 - 2014 Completed:

Division Approved Yes

CSS Applications of Green Chemistry for Sustainable Chemical Processes

CSS 521 521

Michael Gonzalez
NRMRL
STD

Topic/Theme

5 Life Cycle Considerations

Project

5.2 Sustainable Approaches to Chemicals and Processes

Associated Project

None

Task Description

This research effort is to apply a comprehensive life cycle approach to the design and synthesis of sustainable approaches to the production and eventual use of commodity and specialty chemicals. Specialty chemicals include chemicals that may be considered as alternatives to those that possess endocrine disrupting activity or chemicals that are of high importance to the pharmaceutical industry. This research approach will utilize a multitude of concepts including molecular design, the twelve principle of green chemistry, the twelve principles of green engineering principles, the incorporation of benign by design for the use phase, and the application of reverse engineering concepts for the recycle and disposal phases. The ultimate goal is to develop synthesis/manufacturing processes which are more sustainable than its predecessor, with respect to their entire life cycle.

Rationale and Research Approach

Research will be conducted to minimize energy consumption, raw material usage, the number of processing steps, operational and equipment costs, reaction by-products formation, the inherent risks of chemicals and to replace depleting raw materials with renewable resources. The research will also focus on the functionality of a chemical to determine if a substitute chemical can be selected or designed that has inherently less risks while maintaining the desired functionality. The concepts of industrial ecology will be incorporated to determine how waste from one manufacturing process can be utilized by another manufacturing process. Computational techniques, such as molecular design, quantity activity structure activity relationships (QSAR), and chemical intuition will inform laboratory efforts to help optimize the design of the molecules and sustainable process design. To achieve demonstration of these goals and products, this task is broken down into multiple subtasks. The subtasks include: Development of Membranes from Bio-renewable Materials: The separation of hazardous materials from waste streams is a key component of pollution prevention. In addition, the concentration of such materials can allow for recycling in the event these materials must be used in chemical processes. The development of separation systems from renewable materials will increase the sustainability of this aspect of the chemical industry. This subtask focuses on the development of membrane systems synthesized using renewable materials (i.e., cellulose) that can provide both and economic and safe solution to specialty separations for a range of applications. Such a system can be used to impact both the manufacturing and endoflife stages of chemicals. Green Separation Processes for Sustainable Chemical Production: Separation processes account for ~15% of world energy use resulting in significant energyrelated pollutant emissions. Separation processes often generate substantial byproduct wastes such as the solvents used in pharmaceutical manufacturing. Energyand materialefficient separation processes are needed to improve the sustainability of the chemicals, biofuels, and water treatment sectors. The purpose of this subtask is to address the R&D challenges of alternative separations technologies to improve chemical process sustainability with an emphasis on membrane technologies for the purification of solventwater or biofuelwater mixtures. Adoption of more sustainable separation technologies may be limited by the lack of a selective or productive separating agent, the lack of testing under appropriate conditions and scale, or the need to verify performance in a real world environment. Each of these is within the purview of this task. The

energy savings, greenhouse gas reduction, material savings, hazardous chemical reduction, and real world applicability of alternative separation technologies will be evaluated. This task will build upon ongoing research on advanced biofuelwater separation processes through computer modeling and verification experiments with analogue and actual process streams. Scenarios for alcoholbased biofuel and process solvents will be established and modes of integrating the separation process within the heat and mass exchange framework of production facilities will be evaluated. A CRADA for this project is in place through September 2015 with a leading membrane technology provider, Membrane Technology and Research, Inc. (MTR). EPA will partner with potential industrial endusers of research products to integrate separation designs with their processes. Green Synthesis of Nano Materials: This subtask describes green synthesis of nanomaterials using safe, renewable, and biodegradable raw materials such as agricultural waste (red grape pomace, sorghum bran, lemon balm extract etc.). The process of green chemistry and the cappingof nanoparticles with benign materials will enhance their environmental sustainability. These transformations can be accomplished in sustainable manner using magnetically separable and recyclable heterogeneous nanocatalysts with magnetic core. The outer shell (coating) can be of any other metal of choice to accomplish a specific catalytic task in remediation of pollutants of various kinds. This research eliminates the need to use toxic chemicals while producing nanoparticles. These nanomaterials have many Agency relevant applications. One promising application uses nanoscale zero valent iron (NZVI) to promote the breakdown of contaminants in ground water. A CRADA partner has developed innovative cleanup strategies that utilize NZVI and other nonhazardous materials and produce no hazardous waste to help restore contaminated sites back to productive use. Another application uses iron nanoparticles in conjunction with palladium to effectively remediate most of the recalcitrant halogenated materials in soil and water. Another application uses doped mineral oxides (clay) for vapor phase mercury capture from coalfired power plants which ideally suits the requirements of this difficult application in view of the efficiency, robustness and cost. Similarly, affordable fast adsorptive kinetics within a very short contact time which renders these as feasible sorbents in industrial deep desulfurization process for transportation fuels.

Outputs from Projects related to this task

Innovative and comprehensive life cycle approaches for the design and evaluation of sustainable production and use of commodity and specialty chemicals

Expected Products

(3) Demonstration through data and documentation of the successful incorporation and characterization of functionalized nanomaterials in a cellulose membrane domain for specialty separations.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2013

(7) Research documentation and data supporting sustainable nanomaterials to demonstrate greener alternatives to conventional chemical synthesis and transformations using benign media and alternative energy sources such as microwave, ultrasound, mechanochemical mixing and photochemistry.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2014

(1) Joint patent application with CRADA partner for butanol recovery from dilute solutions during manufacturing via membrane-based separation processes in response to the need of OTAQ (OAR) to assess biobutanol as a fuel substitute for bioethanol to potentially lessen greenhouse gas emissions.

Type: OTHER

Delivery Date (FY): 2012

(2) Demonstration of the successful synthesis and characterization of a cellulose membrane with controllable cross-linking for application in sustainable water treatment.

Type: OTHER Delivery Date (FY): 2012

(4) Documentation (including through the patent development) describing greener production of nanomaterials to promote sustainable nanotechnologies and mitigate regulatory needs.

Type: OTHER Delivery Date (FY): 2013

(5) Demonstration and documentation of valorization technologies for the synthesis of higher value products from agricultural waste residues.

Type: OTHER Delivery Date (FY): 2013

(6) Documentation and data describing the toxicological evaluation of green-synthesized nanomaterials.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2014

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

Potential team members include the following: NRMRL: David E. Meyer, Mary Ann Curran, Diana Bless, Raymond Smith, Vasudevan Namboodiri, Michael Gonzalez, Rajender Varma, John Leazer, E. Sahle-Demessie, Tao Li, Tallikapati, Leland Vane, Franklin Alvarez,

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Successful completion of first draft of patent application with patent attorney.	Scheduled: Q3 - 2012 Completed:
(Product 2) Successful synthesis of a cellulose membrane with controllable cross-linking.	Scheduled: Q3 - 2012 Completed:
(Product 2) Completion of film characterization and separation studies for a cellulose membrane.	Scheduled: Q4 - 2012 Completed:
(Product 3) Incorporation of functionalized nanomaterials	Scheduled: Q3 - 2013 Completed:
(Product 4) Identification of compounds to be synthesized	Scheduled: Q3 - 2012 Completed:
(Product 4) Demonstration of synthesis techniques for identified compounds	Scheduled: Q4 - 2012

(Product 4) Characterization of synthesized compounds	Completed: Scheduled: Q3 - 2013
(Product 5) Identification of waste streams to serve as feedstocks for synthesis	Completed: Scheduled: Q3 - 2012
(Product 5) Demonstration of synthesis techniques from identified waste streams	Completed: Scheduled: Q4 - 2012
(Product 5) Characterization of synthesized compounds	Completed: Scheduled: Q3 - 2013
(Product 6) In collaboration with ORD collaborative partner, providing NRMRL synthesized namomaterials for toxicological evaluation	Completed: Scheduled: Q3 - 2013
(Product 6) Upon receiving feedback on evaluation, modification of nanomaterials to address any concerns	Completed: Scheduled: Q4 - 2013
(Product 6) Further evaluation of synthesized nanomaterials.	Completed: Scheduled: Q3 - 2014
(Product 7) Identification of compounds to be synthesized along with technique	Completed: Scheduled: Q3 - 2013
(Product 7) Demonstration of synthesis techniques for identified compounds	Completed: Scheduled: Q4 - 2013
(Product 7) Characterization of synthesized compounds	Completed: Scheduled: Q3 - 2014
	Completed:

Division Approved Yes

CSS Innovation and Technology Management for Sustainable Outcomes

CSS 524 524

Douglas Young
NRMRL
STD

Topic/Theme

5 Life Cycle Considerations

Project

5.2 Sustainable Approaches to Chemicals and Processes

Associated Project

None

Task Description

This task is focused on developing innovative solutions for program office and industrial clients that promote sustainable outcomes by utilizing the concepts of sustainability, life cycle assessment (LCA), green chemistry, and green engineering. The research in this task will be dependent on the collaborations with other governmental entities, academic collaborators, and industrial partners. The outcomes of this task will encompass the entire spectrum of technology management: developing guidelines to quantify the life-cycle environmental performance of a product or process, developing computational tools and approaches to help make this determination, and developing computational and experimental approaches to improve the sustainability of products and processes. The purpose of this research will be to provide tools and approaches that can be used to promote sustainability across the government and industry.

Rationale and Research Approach

The first aspect of this research is to develop guidelines that can be used to quantify the life-cycle environmental performance of a product or process. The use of a life cycle assessment (LCA) based approach for reporting environmental product information is becoming increasingly common for making claims about a products sustainability to inform purchasing decisions. These claims may take the form of single criteria (e.g. product carbon footprint) or multi-criteria (e.g. environmental product declaration) reports or labels. Various general standards exist for making LCA based product claims, but these standards are not specific enough to determine how environmental performance is measured and reported for specific categories of products. For this, more specific guidance is needed, which is defined in ISO 14025 as product category rules (PCRs). Currently, PCRs are being developed independently with inconsistencies that thwart the intention of comparable environmental product information. Groups composed of representatives from governmental agencies, non-governmental organizations, and industry have recognized this potential problem and wish to facilitate the alignment of PCRs for internationally comparable product information. Research will be done to develop common guidelines for PCRs that allow for the generation of comparable environmental product information. The guidelines must be transparent, consistent, and scientifically robust. The second aspect of this research is to develop computational tools and approaches to help determine and communicate the sustainability of a product or process. This effort will focus on taking a holistic (LCA) approach to determine the sustainability of a product or a process by considering the products or processs supply chain in the evaluation. Jointly with an industrial partner, a methodology will be developed to design product supply chains to be as sustainable as possible. This effort will focus on evaluating the sustainability of different industrial manufacturing processes within the same business line. A tool to evaluate the environmental performance or efficiency of a manufacturing process has already been developed by the EPA, the Waste Reduction (WAR) Algorithm. This tool will be expanded to incorporate a broader range of process sustainability tools and metrics for the sustainability evaluation, similar to GREENSCOPE that is being developed in Task 5.2.4, and be integrated into current process simulation software. Once the manufacturing processes have been evaluated, the research will be extended to analyze the sustainability of the supply chains associated

with the products using an LCA framework paired with sustainability metrics. The results of this process will be used to design the most sustainable equipment, operations, and locations for future facilities. This design phase will include developing methodologies for optimizing supply chains for all aspects of sustainability (environmental, social, and economic). This project will provide fundamental information as to (1) what metrics are appropriate for evaluating the sustainability of a supply chain, (2) what are the trade-offs, if any, between sustainability (including social metrics) and economics when designing a new supply chain, and (3) what are the guidelines for designing a supply chain to be as sustainable as possible. The third aspect of this research is to develop computational and experimental approaches to improve the sustainability of products or processes. This aspect will have both computational and experimental activities. From the experimental perspective, research will be conducted in collaboration with industrial partners to help them make their specific chemical manufacturing products in a more sustainable manner. The EPA has developed and continues to develop innovative technologies focusing on the sustainable production of industrially relevant chemicals under process intensified continuous flow conditions. These technologies incorporate the principles of green chemistry and green engineering, such as using renewable raw materials, reducing energy consumption, reducing waste and by-product production, reducing or eliminating the use of hazardous materials (catalysts, solvents, and raw materials), improving atom efficiencies, etc. To assist in the development of sustainable technologies, a software tool, PARIS III, will be developed that will help find less hazardous replacements for industrial solvents. These replacements could be single chemicals or a mixture of chemicals that poses less of a risk. PARIS II was developed for this purpose, but because of legal restrictions the software is unable to be used. The development of the new software will remove these restrictions by using models developed for EPAs TEST software instead of proprietary models.

Outputs from Projects related to this task

Innovative and comprehensive life cycle approaches for the design and evaluation of sustainable production and use of commodity and specialty chemicals.

Expected Products

(12) Process simulation software with integration of the GREENSCOPE indicators tool for use by OCSPP.

Type: DATA
SOFTWARE

Delivery Date (FY): 2016

(4) An international guidance document (with broad international co-authorship) on product category rules for environmental product claims.

Type: PUBLISHED REPORT
GUIDANCE DOCUMENT

Delivery Date (FY): 2013

(5) Beta version of the software tool PARIS III.

Type: DATA
SOFTWARE

Delivery Date (FY): 2013

(6) Process simulation dashboard for with up to 3 sustainability indicators.

Type: DATA
SOFTWARE

Delivery Date (FY): 2013

(7) An evaluation detailing the sustainability issues within the selected process of an industrial partner's business line.

Type: OTHER

Delivery Date (FY): 2014

(8) An evaluation detailing the sustainability issues of the industrial partner's supply chain.

Type: OTHER Delivery Date (FY): 2014

(10) Documentation and methods utilized to demonstrate how to design a hypothetical facility and supply chain to be as sustainable as possible.

Type: OTHER Delivery Date (FY): 2015

(11) Develop a tool to guide industrial entities in developing supply chains to be as sustainable as possible.

Type: OTHER Delivery Date (FY): 2016

(12) Process simulation software with integration of the GREENSCOPE indicators tool.

Type: DATA
SOFTWARE Delivery Date (FY): 2016

(9) Demonstration of continuous flow chemistry to improve a chemical process in collaboration with an industrial partner.

Type: OTHER Delivery Date (FY): 2015

(1) Documentation and data for critical analysis and recommendations for product category rules for environmental product claims.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2012

(2) Fully developed software support tools that includes: (i) Graphical user interface for input and output; (ii) TEST database of chemical properties, thermodynamic activity coefficients, and LCC properties; and (iii) single chemical replacement model.

Type: DATA
SOFTWARE Delivery Date (FY): 2012

(3)Sign CRADA w/an industrial partner to research how to design supply chains to be as sustainable as possible.

Type: EXTRAMURAL DOCUMENT
COOPERATIVE AGREEMENT Delivery Date (FY): 2012

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

Potential team members include the following: NRMRL: Michael Gonzalez, Todd Martin, Paul Harten, William Barrett, Wesley Ingwersen, Jane Bare, Tarsha Eason, Bayou Demeke, Gerardo Ruiz-Mercado, Troy Hawkins, Ray Smith, Mary

External Collaborators (known or proposed)

TBD

Ann Curran, Heriberto Cabezas

Milestones

(Product 1) Progress report on development of recommendations for product category rules (PCR) for product comparison	Scheduled: Q2 - 2012 Completed:
(Product 2) Develop initial graphical user interface	Scheduled: Q3 - 2012 Completed:
(Product 2) Develop required models and databases need for single chemical replacement	Scheduled: Q1 - 2013 Completed:
(Product 3) Come to agreement about the CRADA (including the Statement of Work) with an industrial partner and send the document(s) to the lawyers of both parties for initial review.	Scheduled: Q1 - 2012 Completed:
(Product 4) Report on contribution to international guidance development for product category rule harmonization	Scheduled: Q1 - 2013 Completed:
(Product 5) Develop required models and databases need for mixture replacement	Scheduled: Q3 - 2013 Completed:
(Product 5) Develop alpha version of software	Scheduled: Q4 - 2013 Completed:
(Product 5) Develop beta version of software	Scheduled: Q1 - 2013 Completed:
(Product 6) Develop beta version of the dashboard	Scheduled: Q4 - 2012 Completed:
(Product 7) Produce a list of agreed upon metrics which can be used to evaluate the sustainability of the selected manufacturing process	Scheduled: Q1 - 2013 Completed:
(Product 7) Provide an initial evaluation of the sustainability of the selected manufacturing process	Scheduled: Q4 - 2013 Completed:
(Product 8) Identify the entities that will be included in the sustainability analysis of the supply chain	Scheduled: Q1 - 2013 Completed:
(Product 8) Provide an initial evaluation of the sustainability of the supply chain	Scheduled: Q4 - 2013 Completed:
(Product 9) Develop CRADA relationship with industrial partner to demonstrate application of continuous flow technology to improve the overall sustainability of their chemical process	Scheduled: Q3 - 2012 Completed:
(Product 9) Demonstrate the advantages of a process intensified green chemical reaction strategy to solve an industrial partners current concern	Scheduled: Q4 - 2012 Completed:

(Product 9) Demonstrate the advantages of continuous flow reaction technology with application of green chemistry and engineering principles	Scheduled: Q4 - 2013 Completed:
(Product 9) Demonstrate the advantages of a process intensified green chemical reaction strategy to solve an industrial partners current concern	Scheduled: Q4 - 2014 Completed:
(Product 9) Demonstrate the advantages of continuous flow reaction technology with application of green chemistry and engineering principles	Scheduled: Q4 - 2014 Completed:
(Product 9) Produce a peer-reviewed document demonstrating the quantified advantages and benefits of applying green continuous flow reaction conditions to reactions traditionally performed in a batch reactor scenario.	Scheduled: Q4 - 2015 Completed:
(Product 10) Identify a feasible location(s) for a hypothetical manufacturing facility	Scheduled: Q1 - 2014 Completed:
(Product 10) Define the operating parameters and assumptions that will be used for the sustainability evaluation of a hypothetical facility	Scheduled: Q4 - 2014 Completed:

Division Approved Yes

CSS

Sustainability Indicators for Chemical Processes

CSS 523 523 **Gerardo Ruiz-Mercado**
NRMRL
STD

Topic/Theme

5 Life Cycle Considerations

Project

5.2 Sustainable Approaches to Chemicals and Processes

Associated Project

None

Task Description

The concepts of GREENSCOPE sustainability assessment, process design, integration, and optimization will be incorporated to determine how to minimize raw material consumption and energy loads, while minimizing/eliminating releases, and maintaining the economic feasibility of the process. This research approach will encompass process design from the problem definition to the final design, through all stages of product and process design such as the application of molecular design, incorporation of the twelve principles of green chemistry, carried over to the manufacturing phase to include the use of the twelve green engineering principles, the incorporation of sustainable by design for the use phase, and application of reverse engineering concepts for recycle and disposal phases. This task proposes the early process design stages as the most effective time, with the minimum implementation costs to perform changes having a high potential to influence the sustainability behavior of processes during operation.

Rationale and Research Approach

The finite availability and accelerated depletion of ecological goods and services that sustain societal needs are impelling the chemical industry along a more sustainable path. This new global optimization approach can be addressed through the design of sustainable chemical processes. These sustainable chemical processes must possess the capability to manufacture their valuable product, without negatively affecting the environment or their economic and societal benefits. This can be achieved by altering the amount and type of goods and services (mass and energy) employed and by eliminating the release of pollutants. A main limitation regarding the application of this approach into process development is the assessment of its sustainability. This assessment is required in order to provide guidance, methodology, and tools to designers for the creation of new chemical processes and/or modification of existing designs, all the while proceeding along the path to sustainability. The quantification of process sustainability can be attained through indicators capable of translating chemical process performance and operating conditions into metrics which have significance on a sustainability measurement scale. This Task research project is to develop and implement a sustainability assessment methodology and eventually a multi-operating system software tool called GREENSCOPE (Gauging Reaction Effectiveness for the ENvironmental Sustainability of Chemistries with a multi-Objective Process Evaluator) The GREENSCOPE tool will assist researchers from academia, industry, and government agencies in developing more sustainable chemical processes. Likewise, GREENSCOPE will address extramural input on this topic through collaboration with the NCER centers (see below). This process sustainability assessment assists decision-makers to determine whether a process is more or less sustainable. The sustainability of processes will be evaluated in terms of indicators classified in four main areas (the four Es): Environment, Efficiency (material), Energy, and Economics. GREENSCOPE provides a complete taxonomy and inventory of sustainability indicators classified and defined according to the four E bases in conjunction with a sustainability measurement scale for each indicator. Sustainability assessment using GREENSCOPE is focused on gate-to-gate processes, where the designer has a strong influence. Since sustainability is a holistic approach, belonging to an entire system, a complete sustainability analysis requires an

extensive evaluation of the entire system beyond the manufacturing facility. This can be accomplished through life cycle assessment. The GREENSCOPE sustainability assessment tool will employ process data such as material and energy flows, operating conditions and equipment specifications; properties of the employed substances such as physicochemical, thermodynamic, and toxicity, to evaluate these indicators. Several tools, such as process simulators, pure component property databases, thermodynamic models, equations of state, and experimental measurements can provide the required data for computing GREENSCOPE sustainability indicators. These tools complete the data obtained directly from the analyzed process. Different free online databases are available to provide physicochemical property data and the results of standard toxicology tests (U.S. Environmental Protection Agency; U.S. National Library of Medicine). Governmental organizations such as EPA, NIST (U.S. National Institute of Standards and Technology), OECD (Organization for Economic Cooperation and Development), and the European Chemicals Agency provide online databases for risk and hazard assessment, quantitative structure activity relationships (QSAR) models, physicochemical property databases, prediction and correlation of properties, and environmental, health, and safety (EHS) impact assessment tools. Several EPAs computational tools and database products such as the Aggregated Computational Toxicology Resource (ACToR) database, the Integrated Risk Information System (IRIS) database, the Toxicity Estimation Software Tool (TEST), the Estimation Program Interface (EPI) suite toolbox, the Waste Reduction Algorithm (WAR), and the Tool for the Reduction and Assessment of Chemical and other environmental Impacts (TRACI) will be integrated to GREENSCOPE sustainability assessment tool. The chemical process design problem is performed as a hierarchy of decisions made at different levels such as the batch-versus-continuous production mode, recycle structure, separation system structure, etc. GREENSCOPE approach would permit a sustainability assessment throughout all levels of design in the hierarchy, based on the available data, law restrictions, corporate policies, etc. An early identification and exclusion of less sustainable design options can be performed reducing the complexity on the subsequent detailed design levels. Therefore, if the process sustainability assessment decreases at some level, there are opportunities for process improvements to make topological (arrangement of equipment) and parametric (operating condition) changes without having to obtain a new detailed design. For most process sustainability improvements, a large component of the sustainability performance is attributable to a small fraction of the contributing process design and operating factors. A detailed assessment using GREENSCOPE will help to identify those contributing factors which account for the bulk of the total sustainability performance. Based on a sensitivity analysis of the effects on the sustainability performance, key decision aspects will be identified and chosen. Manifesting an improved sustainability performance requires knowledge of the effect of process design and operating factors on each indicator. With the accomplishment of this work, sustainability assessment using the GREENSCOPE methodology can be proposed and achieved as a reliable and robust tool for the development and optimization of chemical processes. In addition, using GREENSCOPE for a sustainability assessment can provide to the LCA a prediction of the real data needs for process design at early stages, where data availability for conducting an LCA is more difficult to obtain. This Task research work proposes a simultaneous implementation of the GREENSCOPE methodology and LCA for the design of sustainable chemical processes having a global positive impact. Applying GREENSCOPE beyond the gate can lead to reduced complexity of the process, which can allows for potential reduction in data needed for an assessment, prediction of LCA data needs for process design, improvement to the process, and connecting the LCI with the chemists, engineers, and the decision-makers.

Outputs from Projects related to this task

Innovative and comprehensive life cycle approaches for the design and evaluation of sustainable production and use of commodity and specialty chemicals.

Expected Products

(5) Extramural research to advance the science and application of life-cycle thinking and assessment for chemicals (2 STAR Material Life Cycle Safety Research Centers)

Type: EXTRAMURAL DOCUMENT
GRANT

Delivery Date (FY): 2014

(8) Extramural research to advance the science and understanding of sustainable molecular design (2 STAR Sustainable Molecular Design Research Centers).

Type: EXTRAMURAL DOCUMENT
GRANT

Delivery Date (FY): 2017

(3) Demonstration of how the GREENSCOPE sustainability indicator model can implement green chemistry principles through an in-house developed green chemical reaction, which can be applied by OSCPP in educational and evaluation activities and projects.

Type: OTHER

Delivery Date (FY): 2014

(2) Demonstration of how the GREENSCOPE sustainability indicator model can evaluate human health and environmental risks, for an example such as manufacturing of biodiesel.

Type: OTHER

Delivery Date (FY): 2012

(4) Beta version of GREENSCOPE Sustainability Evaluation Tool that can be used to evaluate the impacts of chemicals and processes prior to start up and identify best practices through simulation to comply with potential regulation in a sustainable manner.

Type: DATA
SOFTWARE

Delivery Date (FY): 2014

(1) Demonstration of the application of sustainability principles to a chemical process.

Type: OTHER

Delivery Date (FY): 2012

(6) Description of the integration of GREENSCOPE into LCA for developing globally sustainable chemical production systems.

Type: OTHER

Delivery Date (FY): 2015

(7) Application of process simulation optimization with sustainability indicators to a novel in-house developed green chemistry reaction.

Type: OTHER

Delivery Date (FY): 2016

(3) Demonstration of how the GREENSCOPE sustainability indicator model can implement green chemistry principles through an in-house developed green chemical reaction.

Type: OTHER

Delivery Date (FY): 2014

Start Date Q1 2012

End Date Q4 2016

Cross Research Project Output Supported?
Yes
(SHC)

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)

Potential team members include the following: ORD/NRMRL/STD already directly engaged in precursor work for some percentage of time: Raymond Smith, Michael Gonzalez and moving

External Collaborators (known or proposed)

TBD

forward William Barrett

Milestones

(Product 1) Create a Microsoft Excel draft version of GREENSCOPE	Scheduled: Q2 - 2012 Completed:
(Product 1) Simulate the biodiesel production using an Industrial process simulator	Scheduled: Q2 - 2012 Completed:
(Product 2) Collaborate with the industrial partner on the case study process development	Scheduled: Q3 - 2012 Completed:
(Product 2) Perform a sustainability assessment on the relevant case study	Scheduled: Q4 - 2012 Completed:
(Product 3) Simulate the selected case study process using an Industrial process simulator	Scheduled: Q1 - 2014 Completed:
(Product 3) Perform a full sustainability assessment on the relevant case study	Scheduled: Q2 - 2014 Completed:
(Product 4)Integrate GREENSCOPE to a process simulator	Scheduled: Q4 - 2014 Completed:
(Product 4) Apply GREENSCOPE during all stages of process design for a particular case study	Scheduled: Q4 - 2014 Completed:
(Product 5) Run and depurate Beta-version software tool of GREENSCOPE on a well known chemical process	Scheduled: Q4 - 2014 Completed:
(Product 6) Integrate the Life cycle inventory databases to GREENSCOPE	Scheduled: Q2 - 2015 Completed:
(Product 8) Reports, presentations, and peer-reviewed journal publications identifying inherent chemical attributes associated with hazard risk and novel design strategies to produce useful, environmentally benign chemicals.	Scheduled: Q4 - 2016 Completed:
(Product 8) Development of models that link inherent chemical attributes with hazard, beneficial uses, and associated design strategies.	Scheduled: Q4 - 2016 Completed:
(Product 8) Tools that enable a life cycle accounting of chemicals from design, to production, use, disposal, and/or recycling	Scheduled: Q4 - 2016 Completed:
(Product 9) Simulate the developed green chemical reaction case study at industrial-scale production	Scheduled: Q3 - 2016 Completed:
(Product 9) Obtain the required life cycle inventory data	Scheduled: Q3 - 2016 Completed:

(Product 9) Develop an optimization routine interface based on GREENSCOPE

Scheduled: Q4 - 2016

Completed:

Division Approved Yes

CSS

Dosimetry, Metabolism and PBPK/PD Modeling

CSS 613 613

Rex Pegram and John Nichols
NHEERL
ISTD

Topic/Theme

6 Extrapolation

Project

6.1 Extrapolation from In Silico and In Vitro to In Vivo

Associated Project

None

Task Description

With the rapid development of medium to high-throughput in vitro or small-scale in vivo assays and computational in silico methods to estimate the impacts of environmental chemicals more cost-efficiently, there is a critical need for innovative approaches that can be used to extrapolate these data and predictions to the relevant in vivo setting (e.g., humans or ecological species). Within the CSS Research Program, suites of in vitro assays will be identified that will provide signatures for perturbations of biological pathways (molecular interactions through adverse outcome) that are predictive of toxicities. Such data can be used for chemical prioritization and screening to support programmatic needs (e.g., OWs CCL) and ongoing computational toxicology programs (e.g., EDSP21, TSCA21, OW21), and may provide mode of action data that will inform future targeted and hazard characterization efforts. Research is needed to refine and link in vitro dose-response data and adverse outcome pathway models with physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) models to improve predictions of in vivo dose-response using in vitro results. This task will focus on development of models and methods for: 1) translating predicted and measured in vitro dosimetry and metabolism data to in vivo exposure and target tissue dose scenarios and 2) using in vitro effects data to predict adverse effects in the intact organism, with an emphasis on dose-response relationships. Outcomes of this task include products that will improve and facilitate the interpretation and utilization of in vitro assay results for dose-response determinations, extrapolation, and predictive modeling. This work will help identify circumstances in which in vitro and in silico data can be used to develop biologically-based dose-response models and provide guidance on how this goal may be achieved. These efforts will also make progress toward reducing uncertainty involved in using these types of extrapolations for risk identification and assessment.

Rationale and Research Approach

The primary goal of this task is to reduce uncertainty in the interpretation and extrapolation of data generated by in vitro, small-scale in vivo, and in silico systems designed to test interactions of chemicals with biological pathways or targets. This uncertainty arises because test systems often lack key in vivo processes, such as barriers to absorption, protein binding, and chemical metabolism, which can lead to target cell/molecular dosimetry that is not consistent between the test system and the intact organism. This task will generate products that will directly address these uncertainties, yielding improved approaches for in vitro to in vivo extrapolation (IVIVE) of dose-response relationships for both humans and ecological species. Research approaches for this task can be generally categorized as follows: 1) assessments and translation of in vitro dosimetry in human/mammalian test systems including establishment and use of predictive relationships; 2) research to assess or predict and incorporate in vivo processes (especially metabolism) to improve interpretation/extrapolation of in vitro data; 3) use of PBPK/PD modeling to improve IVIVE of dose-response relationships and predictions of adverse levels of exposures to chemicals; 4) development of a predictive IVIVE system for estimating chemical lifecycle transformations in the environment; and 5) case studies to demonstrate and validate extrapolation methodologies. Additional details for these approaches follow. 1) To maximize the capability of in vitro assays to predict in vivo outcomes, toxicokinetic measures should be incorporated

into the tests and/or coupled with the results as part of the interpretative analysis. For selected mammalian/human assay systems, important factors such as binding of test chemicals to media/culture components, cellular uptake or absorption (intracellular dosimetry), molecular target dosimetry, and xenobiotic metabolism will be analyzed. The use of inherent chemical properties and QSAR for predictive estimates (e.g., effects of lipophilicity and protein binding on absorption) will also be evaluated. This research will focus on developing approaches and data sets needed for IVIVE of results from medium- or high-throughput assays currently being used in ORD. Chemicals will be selected for case studies based on availability of analytical methods and in vivo dose-response data. Another goal is to develop an automated method that allows for determination of partition coefficients (PCs) for ToxCast chemicals. The experimental PC values will be compared with estimates obtained using QSAR techniques. (Products 1,2) 2) Accounting for the impact of chemical metabolism is a critical task for IVIVE, and this research will address metabolism using both experimental and modeling approaches. The overarching issue addressed by the in vitro to in vivo metabolic scale-up research is: what are the utilities and limitations of in vitro extrapolation methods for metabolic rate parameters for IVIVE? This research uses PBPK modeling and data from our in vitro metabolism studies (using both human and rat tissues) along with existing literature data to address multiple specific aims. " Specific aim one is a formal comparison of in vitro compared to in vivo determined rate parameters for environmental chemicals of varying reactivity and solubility. Generation of a database of scaling factors needed to reliably extrapolate in vitro metabolic rate parameters to the in vivo situation coupled with a formal comparison of scaled in vitro metabolic rate parameters with those derived from in vivo studies will substantively address this extrapolation area. " The second specific aim is to refine methodology for IVIVE for metabolic rate parameters based upon our studies. This includes systematic generation of a data base of intrinsic enzyme content and activity factors for both humans and rat strains commonly used in toxicity studies, including characterization of variability to facilitate in vitro scale-up. This second phase also provides stocks of rat microsomes and cytosol from multiple organs (liver, lung, kidney) that can be used to generate chemical-specific parameters for other projects and chemicals of specific interest to the Agency that will be selected based upon consultation with and needs of other projects and organizations within ORD. Innovative approaches for evaluating metabolism using fish and mammalian in vitro systems will be explored. A substrate depletion method for measuring in vitro metabolism rates by fish liver S9 fractions and cryopreserved hepatocytes will be validated. Extrapolation factors required to perform IVIVE of fish metabolism, including hepatocellularity, liver blood flow, and chemical binding in plasma and in vitro metabolizing systems, will be measured. A validated framework will be developed for extrapolating in vitro intrinsic clearance by S9 fractions and hepatocytes to in vivo hepatic clearance in the intact fish. Barriers to absorption will also be assessed examples include studies of dermal absorption and the role of p-glycoprotein in preventing brain and fetal exposures. (Products 2,3) 3) Computational systems models that link real-life exposures to adverse health or ecological outcomes require quantitative analysis of the complex interrelationships between important biological processes and their kinetic and dynamic modulators. This product is based on data generated from in vitro assays to identify modulators for kinetics (e.g. metabolism, transporters, protein binding) and dynamics (e.g. cellular injury, proliferation) to develop PBPK/PD models that link exposure to target tissue dosimetry to specific response markers as identified from in vitro assays in this task and in collaboration with systems models tasks in CSS (AOPs identification and virtual liver and embryo models). Results from the product can also be utilized in linking bioindicators to key events in AOPs for biomarkers research in CSS. (Product 4) 4) The numerous chemical, ecological, and microbiological systems that a chemical or its degradates could encounter during a complete life cycle complicates the assessment and dictates the need for a cross correlated collection of in vitro systems and or models that are representative and predictive of the associated in vivo systems. However, the lack of targeted absorption, metabolism and tissue dosimetry based research creates a source of uncertainty in validating a single in vitro system much less a real world situation composed of numerous in vivo systems that a chemical may encounter during its complete life cycle. Combinations of systems are needed that will be predictive from both an ecological and human health perspective but also need to capture the matrix (soil water food) and species (earthworm, fish, human) dependence. In some cases the metabolism and tissue dosimetry component of this research may need to consider the metabolism of upstream organisms within the food chain and estimate presystemic biotransformation. (Product 5) 5) Case studies that will initially focus on ORD-developed in vitro assays will demonstrate and/or validate extrapolation protocols. One

approach will be to demonstrate a process for determining minimal in vitro data sets needed to accurately model and predict in vivo levels and target tissue dose-response for a range of chemicals and toxicities. An early effort will involve the development and calibration of a PBPK model for lindane (as a case example for a ToxCast chemical) that will be linked to in vivo neurotoxic effects and in vitro micro-electrode array data being generated within NHEERL. (Product 6)

Outputs from Projects related to this task

Validated methods and models that reduce uncertainty in the interpretation and extrapolation of data generated by in vitro, small-scale in vivo, and in silico systems designed to test interactions of chemicals with biological pathways or targets.

Expected Products

(1) Guidance document on the use of predictive relationships to improve in vitro to in vivo extrapolation by evaluating factors that influence intracellular or molecular target dosimetry in vitro (e.g., lipophilicity, solubility in media, protein and non-specific binding).

Type: PUBLISHED REPORT
GUIDANCE DOCUMENT

Delivery Date (FY): 2015

(2) Guidance document on the best practices for use of vitro methods to rapidly assess chemical metabolism and chemical interactions with tissue uptake barriers along with evidence of the predictive use of these results regarding in vivo exposures.

Type: PUBLISHED REPORT
GUIDANCE DOCUMENT

Delivery Date (FY): 2015

(3) A framework utilizing novel data, models and methods that will provide a validated basis for in vitro to in vivo extrapolation of metabolic rate parameters for both humans and ecologically relevant species.

Type: OTHER

Delivery Date (FY): 2015

(5) A system of predictive in-vivo to in-vitro assays that estimate lifecycle transformations and reduce the uncertainty associated with metabolism/tissue dosimetry in PK models.

Type: OTHER

Delivery Date (FY): 2014

(6) Case studies that demonstrate a process for determining minimal in vitro data sets needed to accurately model and predict in vivo levels and target tissue dose-response for a range of chemicals and toxicities.

Type: OTHER

Delivery Date (FY): 2016

(4) Physiologically-based pharmacokinetic/ pharmacodynamic (PBPK/PD) models to reduce uncertainty in dose-response relationships by relating in vitro doses to exposure levels to target tissue levels to adverse outcome pathways (AOPs).

Type: DATA
MODEL

Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NHEERL: Rex Pegram, Elaina Kenyon, Hisham El-Masri, Marina Evans, Tim Shafer, Bill Mundy, Sid Hunter, Stephanie Padilla, Anthony DeAngelo, Michael Hughes, Ed Croom (ISTD Post-doc), Tracey Ross, Joey Yavanxhay, David Ross, Chris Eklund, Randy Harrison,Vicki Richardson, Pat Fitzsimmons, Alex Hoffman, MED post-doc NERL: Jack Creed, Rocky Goldsmith, John Kenneke, Chris Mazur, Satori Marchitti, NCEA: John Lipscomb NCCT: Tom Knudsen, Keith Houck

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Evaluations of factors that influence intracellular or molecular target dosimetry in vitro (e.g., lipophilicity, solubility in media, protein and nonspecific binding): 1) lipid and serum content of in vitro systems and distribution of lipophilic chemicals.	Scheduled: Q4 - 2013 Completed:
(Product 1) Development of an automated method that allows for determination of partition coefficients for ToxCast chemicals	Scheduled: Q4 - 2014 Completed:
(Product 1) Establishment of predictive quantitative relationships for factors that influence intracellular or molecular target dosimetry in vitro to improve IVIVE.	Scheduled: Q4 - 2015 Completed:
(Product 2/3) Validation of substrate depletion method for measuring in vitro metabolism rate by fish liver S9 fractions and cryopreserved hepatocytes	Scheduled: Q4 - 2012 Completed:
(Product 2/3) Measurement of extrapolation factors required to perform in vitro-to-in vivo metabolism extrapolations with fish, including hepatocellularity, liver blood flow, and chemical binding in plasma and in vitro metabolizing systems	Scheduled: Q4 - 2013 Completed:
(Product 2/3) Validated framework for extrapolating in vitro intrinsic clearance by S9 fractions and isolated hepatocytes to in vivo hepatic clearance by intact fish livers	Scheduled: Q4 - 2014 Completed:
(Product 2/3) Methods/data to address the capability of in vitro methods to identify chemical interactions with tissue uptake barriers and test the predictive use of these results regarding in vivo exposures: 1) the importance of p-glycoprotein barrier activity towardsToxcast Chemicals (FY13).	Scheduled: Q4 - 2014 Completed:
(Product 2/3) Report on comparison of in vitro derived and scaled metabolic rate parameters to in vivo derived metabolic rate parameters for a range of environmental contaminants, including identification of limitations and data gaps for current methods.	Scheduled: Q4 - 2015 Completed:
(Product 2/3) Database of hepatic intrinsic factors (e.g., protein and enzyme levels) in liver (microsomes and cytosol) for rat strains commonly used in toxicity studies to provide improved extrapolation factors for IVIVE.	Scheduled: Q4 - 2015 Completed:
(Product 2/3) Database relating hepatic intrinsic factors to those for other organs/tissues (e.g. kidney, lung) in multiple rat strains.	Scheduled: Q4 - 2015 Completed:
(Product 2/3) Report on recommended practices for IVIVE of metabolic rate constants using literature data where the use of generalized scaling factors is necessary.	Scheduled: Q4 - 2015 Completed:
(Product 4) Gathering and combining experimental (in vitro and in vivo) data with	Scheduled:

QSAR models to fill in data gaps for PBPK model development for selected chemicals in collaboration with virtual liver and embryo projects.	Q4 - 2012 Completed:
(Product 4) Linkage of PBPK models with empirical information from AOPs and signature hepatic/embryo effects to develop PBPK/PD models in collaboration with virtual liver and embryo.	Scheduled: Q4 - 2013 Completed:
(Product 4) Improve reverse dosimetry using PBPK/PD models and other high-throughput metrics to estimate environmental exposures resulting in modulations to AOPs.	Scheduled: Q4 - 2014 Completed:
(Product 4) PBPK/PD model development in support of IVIVE of results from ORD in vitro assay systems.	Scheduled: Q4 - 2014 Completed:
(Product 5) Develop a system of in vitro assays that can estimate the biologically relevant exposure to a chemical and its lifecycle degrades and metabolites so that reverse dosimetry approaches can be validated.	Scheduled: Q4 - 2014 Completed:
(Product 5) Estimate life cycle target analyte exposures from relevant pathways and sources using the system of in vitro assay and correlate these estimates with reverse dosimetry estimates calculated using biomarkers	Scheduled: Q4 - 2015 Completed:
(Product 6) IVIVE of neurotoxicity of select ToxCast chemicals	Scheduled: Q4 - 2013 Completed:
(Product 6) IVIVE of developmental toxicity endpoints	Scheduled: Q4 - 2014 Completed:
(Product 6) IVIVE of carcinogenic endpoints	Scheduled: Q4 - 2015 Completed:
(Product 6) Report on case studies that demonstrate proof-of-concept using both in silico and in vitro extrapolation approaches	Scheduled: Q4 - 2016 Completed:

Division Approved Yes

CSS

In Silico to In Vitro and In Vivo

CSS 611 611

Mike Hornung
NHEERL
MED

Topic/Theme

6 Extrapolation

Project

6.1 Extrapolation from In Silico and In Vitro to In Vivo

Associated Project

None

Task Description

The focus of this task is to develop tools that can be used by the Agency to begin to utilize data generated from in vitro assay systems to inform the risk assessment process. The tools developed in this task are aimed at improving our ability to extrapolate the results of in vitro assays to the corresponding in vivo effects by improving our knowledge of the critical parameters that influence the activity of chemicals in these systems. This task also addresses the needs of the Agency for tools for prioritizing and ranking chemicals to be selected for testing in the current EDSP toxicity testing protocols.

Rationale and Research Approach

This task takes a quantitative structure activity relationship (QSAR) approach to understanding the chemical parameters that influence the activity of chemicals. This approach can be applied to both understanding the physico-chemical activities of the chemicals as well as their biological activity, and how these activities are interrelated. In developing these relationships, this project supports EPAs need to evaluate the potential hazard of existing and new chemicals with limited or no toxicity or effects data. The QSAR-based expert system (ES) is one of the types of tools being developed in this task. The QSARbased ES allow risk assessors to predict which chemical structures can initiate specific Adverse Outcome Pathways that the system is built around, and thus sets priorities for targeted testing. An ES is based upon empirical understanding of the properties of chemicals shown to have similar toxicological behavior, and uses this information to extrapolate to untested chemicals. Specifically, this task addresses the need described in the EDSP21 workplan to develop assays and tools for EPA to efficiently evaluate chemicals for endocrine disrupting potential. The QSARbased trout estrogen receptor (ER) binding ES developed in coordination with the Office of Pesticide Programs and used to prioritize and rank fooduse pesticidal inerts for estrogenic potential serves as a proof of concept for building these systems following OECD QSAR validation principles. The approach using strategic chemical selection within targeted EPA inventories will be adapted for testing other species and initiating events in established AOPs. The initial focus will: expand the trout ER-based ES to cover the larger nonfood use inert inventory with assays optimized for chemical properties represented; extrapolate the approach to build a human ER ES; use a focused chemical testing approach to develop an ES for a thyroid synthesis inhibition AOP using frog and mammalian assays; and, deliver the coded rtER ES on a program specific dashboard, as will other expert systems upon completion. In outyrs, additional research and testing will be conducted to provide the data to build ES for additional endpoints, species, and chemical inventories. Extrapolating effects observed in vitro to the effects likely to occur in vivo is currently limited by uncertainty in chemical dose metrics. To begin to close this uncertainty gap, there is a need to develop models to predict the free fraction of chemical in the exposure media that is available to the biological target and understand how chemical properties such as log Kow will affect partitioning between the exposure media and organic components of the assay system (e.g., proteins, lipids). Understanding this partitioning will allow for better extrapolation of dose metrics in vitro to measured or modeled chemical concentrations in vivo. The bioavailability of high log KOW chemicals in these in vitro assays is one area with large uncertainties regarding dosimetry.

Understanding how physical/chemical factors affect parent chemicals will be the basis for work on metabolism described in Tasks 6.1.2 and 6.1.3. These methods will also be tested across a range of assay systems to establish the conservation of these relationships between chemical property and chemical/biological activity across assay systems and species, including fish & mammalian hepatocyte cultures, in vitro cellular fraction-based assays, and cell culture assay systems. Having a sound understanding of how the chemical activity and dosimetry affects in vitro responses is also an important part in developing any scientifically sound Expert System.

Outputs from Projects related to this task

Chemical Class-Based Expert Systems: The output will be expert systems developed using effects-based chemical categories delivered as automated Profilers for use by the Program Offices to predict endocrine disrupting potential of chemicals on defined chemical lists. Applications include EDSP prioritizations and use in hazard assessments of data poor chemicals.

Expected Products

(2) An expert system (hER-ES) based upon human estrogen receptor (ER) binding and transactivation for prioritizing chemicals with endocrine disrupting potential. Linked for delivery to Dashboards.

Type: OTHER Delivery Date (FY): 2013

(3) Develop Framework for extrapolating in vitro to in vivo effects from in silico models based on empirical data that predict unbound chemical concentrations in vitro from inherent chemical properties.

Type: DATA
SCIENTIFIC DATA Delivery Date (FY): 2014

(1) Enhanced Chemical Class-based Expert System (ES) to prioritize endocrine disruption (e.g., estrogen receptor (ER) mediated) potential of food/non-food use pesticide inerts and antimicrobials. Linked for delivery to Dashboards.

Type: OTHER Delivery Date (FY): 2013

(4) A thyroid synthesis inhibition expert system (Thyroid-ES) based upon a thyroid peroxidase inhibition AOP for prioritizing chemicals with endocrine disrupting potential; Linked to delivery to dashboards.

Type: OTHER Delivery Date (FY): 2015

(5)Expert systems (ES) based upon data from human androgen receptor binding and transactivation assays, or additional priority endpoints, species, and inventories, for prioritizing chemicals with endocrine disrupting potential; Linked for delivery to dashboard.

Type: OTHER Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NHEERL: (MED) P. Schmieder, R. Kolanczyk, M.

External Collaborators (known or proposed)

TBD

Tapper, J. Denny, J. Serrano, J. Nichols, A. Hoffman, P. Fitzsimmons (TAD) E. Gray, V. Wilson, S. Laws NCCT: R. Judson

Milestones

(Product 4) Completion of testing antimicrobial list chemicals in the thyroid peroxidase assay for TPO activity inhibition-based Expert System development	Scheduled: Q3 - 2013 Completed:
(Product 4) Completion of testing chemicals for thyroid TPO-based Expert System	Scheduled: Q1 - 2015 Completed:
(Product 1) Completion of testing the remaining non-food use pesticide inert chemicals that will be used in the trout-based ER binding Expert System	Scheduled: Q2 - 2013 Completed:
(Product 2) Compilation of NHEERL and NCCT data for use in developing human ER binding Expert System.	Scheduled: Q1 - 2013 Completed:
(Product 1/2) Delivery of trout and human ER Expert Systems to Dashboard	Scheduled: Q4 - 2013 Completed:
(Product 3) Empirical algorithms to predict free chemical concentration as a function of log Kow in fish in vitro metabolizing systems	Scheduled: Q1 - 2014 Completed:

Division Approved Yes

CSS

In Vitro to In Vivo Exposure and Effects

CSS 612 612

Susan Laws
NHEERL
MED

Topic/Theme

6 Extrapolation

Project

6.1 Extrapolation from In Silico and In Vitro to In Vivo

Associated Project

None

Task Description

This task will provide extrapolation tools, methods, and models needed to utilize data from medium- and high-throughput in vitro screening assays in both human health and ecological risk assessments. Although dose-response relationships are generally considered in the context of whole-organism responses, the principles that underlie these relationships also apply to in vitro testing efforts. Thus, challenges associated with extrapolating in vitro data to the intact organism generally relate to uncertainty regarding toxicologically relevant chemical concentrations in vitro and vivo (dosing uncertainty) or the extent to which effects observed in vitro reflect in vivo effects occurring at the same effective dose (effects uncertainty). Research performed under this task will address both of these fundamental sources of extrapolation uncertainty. Additional research will be conducted to relate measured contaminant levels in water (e.g., municipal effluents) to in vitro and in vivo bioassay results, thereby linking in vitro, in vivo, and environmental exposures.

Rationale and Research Approach

A significant challenge when performing in vitro-to-in vivo effects extrapolations is the need to relate the effective in vitro dose to that achieved at the site of action in the intact organism. Currently, in vitro effects information is generally related to a measured or nominal concentration. Typically, the unbound chemical concentration provides a stronger basis for extrapolation, since this is the concentration that is freeto exert adverse effects. The unbound fraction that exists within an in vitro system is a function of the components of that system and may differ substantially from that in vivo. This discrepancy creates a need to measure the unbound concentration and relate this to the measured or predicted unbound concentration in vivo. Products 2 and 5 will focus on the development of novel methods for measurement and control of unbound chemical concentrations in vitro, and a framework for relating this information to the intact organism. Passive sampling methods (Solid Phase Microextraction SPME) will be used to measure unbound chemical concentrations in commonly employed in vitro metabolizing systems (S9, hepatocytes). Existing algorithms that predict in vivo equilibrium blood and tissue partitioning from inherent chemical properties (e.g., log KOW) will then be used to create the in vitro-in vivo dosimetry linkage. Controlled in vitro dosing methods will be developed by using a passive partitioning phase (typically PDMS-silicon) as the source of chemical for in vitro bioassays. Once perfected, this approach could be used to conduct in vitro experiments at chemical concentrations measured in vivo or predicted from pharmacokinetic modeling efforts. Uncertainty regarding extrapolation of in vitro effects to the intact organism derives from the incomplete nature of such assays with respect to the presence and activities of relevant biochemical processes and their ability to represent complex responses of the intact organism. Research is needed, therefore, to determine the strengths and limitations of in vitro assays so that the resulting data can be confidently related to an expected in vivo outcome. Product 7 describes research needed to develop medium- and high-throughput in vitro assays for chemicals that have adverse impacts on the nervous system. Neurophysiological assessments will be performed across three levels of biological complexity - output of neurons in culture, output of brain slices with a maintained neural circuitry, and output in brain recordings from intact animals - to assess impact of chemicals on nervous system function. The ability

of chemically-induced alterations in neurophysiology of cell-based assays to predict outcomes measures in more complex systems will be determined. Pesticides and other test chemicals will be selected based on mode-of-action and toxicity pathways in consultation with NCCT and proposed Systems Biology Projects. Initial experiments will optimize procedures, parameters, and endpoint selection across preparations to allow direct linkages between in vitro and in vivo effects. Once established, application of these models to assess developmental neurotoxicity and tissue dosimetry will be addressed. Products 1, 3, 4, and 6 address the issue of potential exposure of non-target species to endocrine active pharmaceuticals (EAPs) using an approach that relies on both effects and exposure extrapolation. A need exists to develop methods for measurement of the EAPs to which humans and wildlife are exposed. Novel methods, including the use of passive sampling devices, will be developed to measure EAPs in effluents and receiving waters. Additional research is designed to translate measured exposures into predictions of chemical uptake and accumulation. Of special concern is the role of sex hormone binding globulins (SHBG) in promoting uptake and retention of specific endocrine-active compounds by non-target species (e.g., fish). Although SHBGs are expressed by all vertebrates, their binding properties vary among species. Different species may also differ with respect to their ability to metabolize these compounds. In vitro and in vivo work will be conducted to characterize these species differences. Exposure data will be linked to predicted molecular targets for groups of EAPs (e.g., cellular and biochemical endpoints) and adverse outcomes (e.g., fish reproduction) using in vitro and in vivo approaches. This information will then be used to predict likely adverse outcomes on non-target species based on their environmental exposure and the presence/absence of relevant molecular targets. Finally, in vitro assays, suitable for the evaluation of an EAP alone, or in mixtures, will be used to evaluate effects of environmentally relevant mixtures of EAPs. These products will provide tools for extrapolation of both effects and exposure information for a high priority class of emerging chemical contaminants.

Outputs from Projects related to this task

Methods and models to apply in vitro and in silico derived data to individuals.

Expected Products

(5) Guidance document on the use of passive dosing methods to control the dose of hydrophobic compounds in in vitro assays and serve as a chemical source for in vitro metabolism assays.

Type: PUBLISHED REPORT
GUIDANCE DOCUMENT

Delivery Date (FY): 2014

(6) Guidance on extrapolation of data from medium and high throughput assays to adverse neurophysiological effects in vivo.

Type: OTHER

Delivery Date (FY): 2014

(7) Environmentally relevant exposure metrics for groups of endocrine active pharmaceuticals in effluents and receiving waters linked to predicted molecular targets and adverse outcomes in non-target species.

Type: DATA
SCIENTIFIC DATA

Delivery Date (FY): 2015

(1) Integrated method linking endocrine active pharmaceuticals (EAPs) exposure (environmental concentrations) with biological effects observed in in vitro and in vivo assays (to support program offices).

Type: OTHER

Delivery Date (FY): 2013

(2) Novel methods to measure unbound chemical concentrations in vitro and a framework to reduce uncertainty when extrapolating from in vitro to relevant in vivo exposures.

Type: OTHER

Delivery Date (FY): 2013

(3) Guidance document on the use of in vitro data for predicting biological effects of exposures to endocrine active pharmacuetical in non-target species.

Type: PUBLISHED REPORT
GUIDANCE DOCUMENT

Delivery Date (FY): 2014

(4) Toolbox of analytical chemistry methods that identify and quantify EAPs plus major metabolites in aqueous samples (waste water, surface waters) and plasma. Sampling strategies (e.g, grab samples versus polar organic chemical integrated samplers (POCIS)) for EAPs will be included.

Type: OTHER

Delivery Date (FY): 2014

Start Date Q1 2012

End Date Q4 2015

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NRMRL: Marc Mills NHEERL: John Nichols, Patrick Fitzsimmons, Alex Hoffman, MED Post-doc, David Herr, Mary Gilbert, Tim Shafer, Danielle Lyke, Andrew Johnstone, Cina Mack, TAD Post-doc, Lesley Mills, Susan Laws, Michelle Hotchkiss, Saro Jayaraman, Ruth Gobell, Dodi Borsay NERL: Tammy Jones-Lepp, Matthew Henderson

External Collaborators (known or proposed)

TBD

Milestones

(Product 6) Application of neuronal-function-based metrics to determine sensitivity of a cell-based assay to predict ex vivo and whole animal neurotoxicity caused by neurotoxic pesticides	Scheduled: Q4 - 2012 Completed:
(Product 1/4) Method for detecting selected endocrine-active pharmaceuticals in environmental water samples and fish plasma	Scheduled: Q4 - 2012 Completed:
(Product 3) Case study with endocrine-active pharmaceuticals to determine both environmental concentrations and biologically-active exposure levels for a non-target species (e.g., fish)	Scheduled: Q4 - 2013 Completed:
(Product 2) Method for measuring the unbound concentration of a hydrophobic compound in different in vitro test systems and a framework for extrapolating this information to the intact organism	Scheduled: Q4 - 2013 Completed:
(Product 5) Method for controlled dosing of hydrophobic compounds in selected in vitro bioassay systems	Scheduled: Q4 - 2013 Completed:
(Product 6) Identification of optimal methods and metrics to extrapolate effects across neurons in culture, brain slices, and whole animal brain recordings	Scheduled: Q4 - 2013 Completed:
(Product 4) Toolbox of analytical methods for identification and quantitation of endocrine-active pharmaceuticals and their major metabolites in environmental water samples and plasma, including sampling strategies for measurement of	Scheduled: Q2 - 2014 Completed:

pharmaceuticals that are present in water at very low concentrations

(Product 7) Comparison of the metabolism of selected endocrine-active pharmaceuticals across species and the impact of species differences on the ability of in vitro assays to predict adverse outcomes in vivo	Scheduled: Q4 - 2014 Completed:
(Product 5) Demonstrated application of controlled dosing methods to measure in vitro metabolism rates for hydrophobic environmental contaminants	Scheduled: Q2 - 2014 Completed:
(Product 6) Application of neuronal-function-based metrics in cells and brain slices to identify developmental neurotoxicity	Scheduled: Q2 - 2014 Completed:
(Product 6) Evaluation of consistency of findings across chemical classes in cell-based assays to predict developmental neurotoxicity in vivo	Scheduled: Q4 - 2014 Completed:

Division Approved Yes

CSS Develop Quantitative Models to Extrapolate between Subpopulations Segregated by Life-Stage or Age Group

CSS 622 622

Glen Thursby
NHEERL
AED

Topic/Theme

6 Extrapolation

Project

6.2 Extrapolation of Individual and Population Endpoints

Associated Project

None

Task Description

The focus of this task is to provide biologically and environmentally relevant context for risk assessments of current and future chemical contaminants. Successful completion of the research will significantly reduce the uncertainty associated with these risk assessments, which in turn will improve their reliability. This improved reliability further contributes to the sustainable use of chemicals in the environment by minimizing potentially costly mistakes (both environmental and economical) from either under- or over-protection. The research specifically will focus on methods of using existing requirements for toxicological data to integrate multiple endpoints from exposure to different life stages under the conditions of time varying toxicant concentrations.

Rationale and Research Approach

Evaluation of different aquatic exposure scenarios is an integral part of EPAs risk assessment process for the registration or re-registration of pesticides. While OPP has research needs associated with exposure models (e.g, incorporation of spatial variability in exposure parameters or development of urban and residential aquatic exposure models), there also is a need to better link time-varying exposure to population-level effects. Currently, OPP generates a 30-year, daily estimate of concentration and then compares acute or chronic effects values for the most sensitive species in a taxonomic group to various aspects of expected environmental concentrations. This process does not account either for cumulative impacts of multiple lowexposures to the same chemical over time (potential for under protection) or recovery rates after a short highexposure (potential for over protection). The current approach also does not account for overlapping the life history strategy with exposure scenarios (e.g., accounting for whether or not key life events such as reproduction occur during the time of highest likelihood of exposure. The incorporation of toxicokinetic/toxicodynamic modeling within periodic matrix models would provide a more realistic evaluation of exposure scenarios by allowing the use of all of the exposure data, as well as incorporating the seasonality of spawning and the presence of more sensitive life stages. The use of periodic matrix models also allows any species, no matter what the duration of its life history (weeks, months or years), to be evaluated based on the probability of an adverse effect using the same time frame (i.e., annual). The specific deliverable is currently envisioned to be an MS Excel-based population model that will evaluate time-varying exposure concentrations for any species for which OPPs standard toxicity effects data are available. Many of OPPs current models are Excel-based. Thus, the time needed to learn the use of this new model would be minimal. Although the initial effort will be with an Excel-base model, this task also will evaluate the utility of transferring the model to a web-based platform. If successful, the use of a web-based model will eliminate potential issues associated with backward compatibility as the Agency moves to newer versions of the Excel software, as well as enhance accessibility. The model will not require any additional data other than that typically provided to OPP during the registration process, and would build upon a previously delivered laboratory-based population matrix model. The output from the model should be easily incorporated into OPPs standard Environmental Fate and Ecological Risk Assessment documents within the chapter on Risk Characterization. One important question that the research will address will be whether or not the use

of population models of this type will have added value to OPPs current risk management decisions. Therefore a key element of the work is closely working with OPP to ensure the ultimate model is appropriate to their risk assessment (and risk management) needs. As a part of the deliverable, the project will provide OPP with boiler platelanguage for potential inclusion in their standard templates. The modeling effort will provide a different approach to how OPP could evaluate the effects of pesticides on aquatic populations. First, it will allow combining acute and chronic effects into a single population-level endpoint. Second, the use of an annual periodic matrix model (with weekly or monthly sub-matrices) evaluates all aquatic species using the same time-step. Current practice evaluates endpoints (e.g., LC50s) for species with vastly different life history strategies. Use of periodic matrix models as the basis of risk evaluation can normalize for these different strategies by allowing a common currencyto be used (e.g., probability of an X% reduction in the expected population size at the end of the year). The use of this new assessment procedure will contribute to minimizing the likelihood of over or under protection decisions that may occur due to an inability to realistically incorporate time-varying exposures in the risk assessment process. The more accurate the evaluation of allowable pesticide application, the more sustainable their continued use.

Outputs from Projects related to this task

Develop quantitative models to extrapolate between subpopulations segregated by life-stage or age group.

Expected Products

(1) Population model for evaluting time-varying exposure concentrations for species with OPP toxicity effects data (MS Excel-based).

Type: DATA
MODEL

Delivery Date (FY): 2014

(2) Guidance for using population modeling endpoints in risk assessments for any aquatic animal species for which they may have traditional toxicity data--includes an MS Excel model for deriving default population demographic parameters (survival rates for different life stages and fecundity rates) for when such data are not readily available.

Type: PUBLISHED REPORT
GUIDANCE DOCUMENT

Delivery Date (FY): 2014

Start Date Q1 2012

End Date Q4 2015

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NHEERL: S Rego, J Copeland; OCSPP: Keith Sappington

External Collaborators (known or proposed)

TBD

Milestones

None

Division Approved Yes

CSS

Extrapolation from Individuals to Populations

CSS 623 623

Rick Bennett
NHEERL
MED

Topic/Theme

6 Extrapolation

Project

6.2 Extrapolation of Individual and Population Endpoints

Associated Project

2.4 Systems Approaches to Assess Human and Ecological Risks

Task Description

The focus of this task is to develop and deliver models for translating wildlife toxicity test data into a currency useful for population-level risk assessments by estimating the magnitude of change in demographic parameters (i.e., survival and fecundity rates) resulting from specific chemical exposure scenarios. Toxicity translator models integrate toxicity test endpoints with information on life history characteristics of a species of concern and the timing of chemical exposure during its breeding season. While it is important that toxicity translator models are parameterized using data from existing toxicity tests, there are new or modified toxicity tests currently being evaluated for inclusion in the ecological risk assessment process. An experimental portion of this task will explore how improvements in the experimental design of fish toxicity tests and incorporation of new endpoints increase understanding of Adverse Outcome Pathways (AOP) and improve the ability of toxicity translator models to quantify effects on demographic parameters.

Rationale and Research Approach

The Office of Pesticide Programs (OPP) has made a priority of improving their ecological risk assessment process to better quantify the probability and magnitude of risks to populations of species of concern. While the existing battery of laboratory toxicity tests provides a suite of test endpoints reflecting specific toxicological responses, none of the endpoints are in the same currency as the demographic parameters (i.e., annual survival and fecundity rates) needed for population-level assessments. Modeling approaches are needed to integrate available toxicity data with information on species life history and the timing of potential chemical exposure in model simulations to estimate the change in survival and/or fecundity rates resulting from defined exposure scenarios. In the Adverse Outcome Pathway framework, toxicity translator models provide the tools necessary to move from the individual level to the population level by providing population modelers with the data needed on changes to demographic parameters. These toxicity translator models also provide information on which species (or life history characteristics) are at greatest risk from a specific exposure scenario or what exposure scenarios have the greatest impacts on a species of concern. Toxicity translator models would be produced for the vertebrate taxonomic groups currently evaluated in ecological risk assessments initially fish and birds, though OPP is interested in extending concepts to mammals and amphibians -- along with supporting users manuals and technical support manuals. The development of toxicity translators requires integration of work on chemical toxicity testing and exposure assessment with ecological systems modeling. By improving the quality of ecological risk assessments to more clearly describe the potential risks to free-ranging populations, toxicity translators are designed to provide risk managers with tools for assessing how a specific chemical-use scenario affects the population sustainability of species of concern. Models would be designed to use data currently available to OCSPP risk assessors and other program offices, and would be flexible enough to incorporate data from new toxicity tests and assays developed through the CSS research program as appropriate. Along with model development, experimental research will continue to improve the design of laboratory toxicity tests and develop new sub-organismal endpoints that will increase our ability to identify adverse effects and be instrumental in our understanding of Adverse Outcome

Pathways (AOP). Small fish are especially useful for developing AOPs for vertebrate reproduction due to the ability to rigorously characterize exposure in laboratory tests and the short reproductive development times. Furthermore, measurements at lower-levels of biological organization, from molecular to pathology effects, are easily incorporated into the test protocols. Growth and reproductive outcomes such as fecundity and fertility are the primary apical endpoints of the full life-cycle fish tests. Linking effects measured at lower-levels of organization such as gene expression profiles and histopathology with reproductive outcomes provides insight into important adverse outcomes at the individual level. Additionally, these apical outcomes at the individual level, can inform toxicity translator modules for important population-level risk assessment models. Ultimately this research will provide a better understanding of AOPs of vertebrate reproduction. This understanding will help inform the development of better test strategies and extrapolation models. Outputs of this task will be integrated into the wildlife population modeling within CSS Systems Models project 2.4.

Outputs from Projects related to this task

Methods and models to extrapolate endpoints with and among individuals and populations.

Expected Products

(1) Develop avian toxicity translator model for extrapolation from individual to population level effects (basic version, MCnest) including users manual and technical support manual.

Type: DATA
MODEL

Delivery Date (FY): 2013

(2) Basic version of a fish toxicity translator model for extrapolation to population level effects along with users manual and technical support manual.

Type: DATA
MODEL

Delivery Date (FY): 2014

(3) Report on the relationships between early gene expression, growth, pathology and reproductive outcomes in fish exposed to chemicals with various AOPs.

Type: PUBLISHED REPORT
REPORT

Delivery Date (FY): 2014

(4) Evaluate the sensitivity of fish toxicity translator models to various test parameters, endpoints such as growth dynamics, gene expression, and pathology, and life history strategies.

Type: DATA
MODEL

Delivery Date (FY): 2015

(5) Advanced version of an avian toxicity translator model for extrapolation to population level effects (MCnest) along with users manual and technical support manual.

Type: DATA
MODEL

Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

External Collaborators (known or proposed)

Potential team members include the following: NHEERL: M. Etterson, A. Olmstead, R. Johnson, J. Hoffman, P. Schmieder, and D. Hoff, plus S. Degitz and D. Villeneuve in out-years on fish assay research NERL: TBD as exposure options are refined in out-years	TBD

Milestones

(Product 1) Draft version of avian toxicity translator model including users manual and technical support manual	Scheduled: Q4 - 2012 Completed:
(Product 2) Draft version of fish toxicity translator model including users manual and technical support manual	Scheduled: Q2 - 2014 Completed:
(Product 3) Draft report on relationships between early gene expression, growth, pathology and reproductive outcomes in fish exposed to chemical with various AOPs.	Scheduled: Q1 - 2014 Completed:
(Product 4) Draft sensitivity analysis of fish toxicity translator models to various test parameters	Scheduled: Q1 - 2015 Completed:
(Product 5) Draft version of avian toxicity translator model integrated with outputs of OPPs Terrestrial Investigation Model (TIM)	Scheduled: Q3 - 2014 Completed:
(Product 5) Analysis of methods for improving the simulation of avian breeding season length in the avian toxicity translator model	Scheduled: Q1 - 2015 Completed:

Division Approved Yes

CSS

Extrapolation within and among Individuals

CSS 621 621

Jill Awkerman
NHEERL
GED

Topic/Theme

6 Extrapolation

Project

6.2 Extrapolation of Individual and Population Endpoints

Associated Project

None

Task Description

Predictive toxicity models have been used to develop and refine tools for estimating species sensitivity of aquatic organisms and wildlife to pesticides and other contaminants in support of OCSPP ecological risk assessments and biological evaluations performed by OW and Regions. Updates to interspecies extrapolation model utilities under this task include development of new mode of action (MOA)-based toxicity estimation models and developing standardization for species sensitivity distributions using acute toxicity databases.

Rationale and Research Approach

For ecological risk assessments and biological evaluations conducted under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Clean Water Act (CWA) predictive toxicological models are required to maximize the usefulness of limited information to protect a broad array of aquatic and wildlife species, including endangered species and those that have not been tested or are not feasible to test. The Interspecies Correlation Estimation (ICE) database provides a resource of acute toxicity data (e.g. LC/EC50, LD50) to estimate toxicity for under-represented taxa. The expansion, validation, and refinement of ICE models have been on-going to provide a defensible and versatile tool for ecological risk assessments. The Web-based Interspecies Correlation Estimation (Web-ICE) application was developed to provide direct access to ICE models, provide quick and efficient model updates, and expand the ICE user base to national and international agencies, risk assessors and risk managers. Additional research and development for Web-ICE will include an expanded database with specific focus on endangered species, and deployment of an algal toxicity database and toxicity estimation module. OCSPP has requested that ORD develop MOA-based ICE models to allow interspecies toxicity extrapolation for specific groups of chemicals such as acetylcholinesterase inhibitors. A complimentary Inherency project (1.3.1) will develop an MOA assignment methodology and MOA database in collaboration with NRMRL, NERL, NCCT, and other NHEERL divisions. This extrapolation task first will use existing MOA assignments to develop preliminary MOA-based ICE models, then will utilize the Inherency MOA database to provide definitive MOA-based ICE models to OSCPP via the Web-ICE internet tool. Generating species sensitivity distributions (SSD) is another approach that allows toxicity estimation for a range of diverse species. Specifically, a cumulative distribution function determines the toxicity value for a specified percentile of species. The HD5, for example, is a hazard dose lower than the LD50 value for 95% of the represented species. Maximizing sample size necessitates inclusion of all available species data when developing SSD; therefore, hazard dose estimates among species frequently overlook biological or taxonomic processes that influence susceptibility within the species represented. Further investigation of both the modeling methods that influence SSD extrapolation and the underlying causes of variability in toxicity among species will refine toxicity estimations and provide further guidelines for use of the ICE SSD component as well as SSD development and species toxicity relationships in general. Analyses of sources of variance in toxicity data will further guide investigations on intrinsic factors affecting susceptibility in aquatic and wildlife species that may be related to physiology, taxonomy, and mode of action. Examination of model fitting methods and error propagation in SSD development will

also guide studies of toxicity extrapolation. Following reports on intrinsic differences in species sensitivity and model fitting methods, a comprehensive guide to SSD development within ICE will be a contribution to the website. Research planned for this task includes three projects: 1) expansion and refinement of Web-ICE database and toxicity estimation models, including algal toxicity estimation module, 2) development of MOA-based models for interspecies extrapolation, and 3) providing comprehensive guidance on data standardization and optimal SSD development.

Outputs from Projects related to this task

(1) Expanded database and algal toxicity estimation module. (2) MOA-based ICE models. (3) SSD guidance for data standardization and methods to reduce uncertainty.

Expected Products

(1) Develop interspeices Mode-of-Action extrapolation models for predicting acute toxicity in untested species from surrogate species (made available to Program Offices through Web-ICE).

Type: DATA
MODEL

Delivery Date (FY): 2012

(2) Recommendations on data standardization and species diversity optimization for developing chemical toxicity species sensitivity distributions.

Type: OTHER

Delivery Date (FY): 2014

(3) Comprehensive guidelines for SSD development using ICE database

Type: OTHER

Delivery Date (FY): 2014

Start Date Q1 2012

End Date Q4 2014

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NHEERL (GED): M Barron, S Raimondo, C Jackson

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Develop preliminary interspecies Mode-of-Action extrapolation models for predicting acute toxicity in untested species from surrogate species (made available to Program Offices through Web-ICE)	Scheduled: Q3 - 2012 Completed:
(Product 2) Analysis of data standardization and species diversity effects on SSD	Scheduled: Q2 - 2013 Completed:
(Product 3) Analysis of SSD development using ICE database	Scheduled: Q2 - 2014 Completed:

Division Approved Yes

CSS

Development of Decision Support Tools Based on Program Office Needs and Sound Science, to Support Regulatory Uses

CSS 714

714

David Reif
NCCT
IO

Topic/Theme

7 Dashboards

Project

7.1 Program-Specific Decision Support Tools on Dashboards

Associated Project

None

Task Description

By building Program-specific dashboards, this task will serve Program Office needs for the endocrine disruptor screening program (EDSP21), FIFRA and FQPA implementation (OPP21), TSCA implementation (TSCA21), SDQA implementation (OW21), and Human Health Risk Assessment (HHRA21). By establishing and implementing a process for translating ORD tools into Program Office needs, this task links tools and models produced from any CSS topic area into Program-specific dashboards.

Rationale and Research Approach

It is vital to integrate the output of CSS research into coherent decision-making contexts supporting needs that include prioritization, targeted testing, mode-of-action assessment, and dose-response characterization. This task will deliver actionable information about chemicals and other stressors in the form of customizable dashboards in order to meet specific EPA Program Office (PO) needs for chemical programs (EDSP21, TSCA21, OW21, OPP21, and HHRA21). The dashboards consolidate information from disparate sources as collections of flexible, visual widgets, where individual widgets synthesize information according to user specifications. For example, widgets could be created for the Virtual Tissues Knowledge Base (VT-KB), Toxicological Prioritization Index (ToxPi), or ER Expert System. Widgets will then be combined into PO-specific dashboards, where PO partners can customize the information displayed to support diverse decision-making tasks. The use of such a customizable framework allows information from multiple sourcesincluding ToxCast in vitro bioactivity profiles, in vivo animal toxicity results, inferred toxicity pathways, exposure predictions, chemical properties/descriptors, and other outputs from CSS projectsto be recombined into comprehensive profiles according to programmatic needs. Thus, the dashboards allow inherently multivariate assessment of risk across all sectors of concern for any set of chemicals. The tools for developing dashboards will be extensible, in order to incorporate existing and new types of data (e.g. measures of biotransformation, exposure, dosimetry), novel widgets, and PO requests. Ultimately, the 21st-Century workplan dashboards will allow rapid incorporation of computerized data, new and old, into regulatory decisions, including metrics for statistical confidence in decisions. The strategic approach for completing this task includes the following components (sub-tasks/aims): 7.1.4.1: Development and implementation of new databases and tools required for program-specific dashboards (e.g. AOP database/EffectoPedia or capture of EDSP Tier 1 assay results). 7.1.4.2: Prototype versions of web-based dashboards for evaluating screening, testing, exposure and sustainability information relevant to EDSP21 (potential endocrine disruption), OPP21 (pesticidal actives, inerts and antimicrobials), TSCA21 (prioritizing and assessing new and existing chemicals), OW21 (prioritization of chemicals for the PCCL/CCL and other purposes), HHRA21 (PPRTV and NexGen risk assessments). 7.1.4.3: Regular updates (6-month cycles) of all PO web-based dashboards, taking into account user feedback and new scientific developments.

Outputs from Projects related to this task

The outputs from this task are initial prototype dashboards, followed by regular updates. The first

outputs will be prototype versions of web-based dashboards for evaluating screening, testing, exposure and sustainability information relevant to EDSP21 (potential endocrine disruption), OPP21 (pesticidal actives, inerts and antimicrobials), TSCA21 (prioritizing and assessing new and existing chemicals), OW21 (prioritization of chemicals for the PCCL/CCL and other purposes), HHRA21 (PPRTV and NexGen risk assessments). The next outputs will be regular updates (6-month cycles) of all PO web-based dashboards, taking into account user feedback and new scientific developments.

Expected Products

(1) Plan for development of new databases and tools required for the development of program-specific dashboards (e.g. AOP database/EffectoPedia)

Type: OTHER Delivery Date (FY): 2012

(2) Program-specific dashboard related to Adverse Outcome Pathways.

Type: DATA
SOFTWARE Delivery Date (FY): 2013

(3) Prototype version 1.0 of web-based dashboards followed by updates every six months including: EDSP21 (Endocrine Disruptor Screening Program for the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to potential endocrine disruption.

Type: DATA
SOFTWARE Delivery Date (FY): 2012

(4) Prototype version 1.0 of web-based dashboards followed by updates every six months including: OPP21 (Office of Pesticide Programs for the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to pesticidal actives, inerts and antimicrobials.

Type: DATA
SOFTWARE Delivery Date (FY): 2012

(5)Prototype version 1.0 of web-based dashboards followed by updates every six months including: TSCA21 (Toxic Substances Control Act for the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to prioritizing and assessing new and existing chemicals.

Type: DATA
SOFTWARE Delivery Date (FY): 2012

(6) Prototype version 1.0 of web-based dashboards followed by updates every six months including: OW21 (Office of Water for the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to prioritization of chemicals for the PCCL/CCL and other purposes.

Type: DATA
SOFTWARE Delivery Date (FY): 2012

(7) Prototype version 1.0 of web-based dashboards followed by updates every six months including: HHRA21 (Human Health Risk Assessment in the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to PPRTV and NexGen risk assessments.

Type: DATA
SOFTWARE Delivery Date (FY): 2012

(8) Updated versions of web-based dashboards every six months: EDSP21

Type: DATA SOFTWARE — Delivery Date (FY): 2016

(9) Updated versions of web-based dashboards every six months: OPP21

Type: DATA SOFTWARE — Delivery Date (FY): 2016

(10) Updated versions of web-based dashboards every six months: TSCA21

Type: DATA SOFTWARE — Delivery Date (FY): 2016

(11) Updated versions of web-based dashboards every six months: OW21

Type: DATA SOFTWARE — Delivery Date (FY): 2016

(12) Updated versions of web-based dashboards every six months: HHRA21

Type: DATA SOFTWARE — Delivery Date (FY): 2016

(13) EDSP DER Composers for capture of Tier 1 assay results to populate OPP database are delivered.

Type: OTHER — Delivery Date (FY): 2012

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NCCT: David Reif, Richard Judson, Imran Shah, Matt Martin, John Wambaugh NHEERL: Pat Schmieder, Dan Villeneuve, Mike Hornung NERL: Carry Croghan, Tom Purucker, Jack Jones

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Requirements document for new databases and tools	Scheduled: Q3 - 2012 Completed:
(Product 2) DER Composer Prototype v1.0	Scheduled: Q3 - 2013 Completed:
(Product 3) AOP Dashboard Prototype v1.0 for AOPs	Scheduled: Q1 - 2013 Completed:
(Product 4) Prototype version 1.0 of EDSP21 Dashboard	Scheduled: Q2 - 2012 Completed:
(Product 4) Version 2.0 of EDSP21 Dashboard	Scheduled: Q4 - 2012 Completed:

(Product 4) Version 3.0 of EDSP21 Dashboard	Scheduled: Q2 - 2013 Completed:
(Product 4) Version 4.0 of EDSP21 Dashboard	Scheduled: Q4 - 2013 Completed:
(Product 5) Prototype version 1.0 of OW21 Dashboard	Scheduled: Q2 - 2012 Completed:
(Product 5) Version 2.0 of OW21 Dashboard	Scheduled: Q4 - 2012 Completed:
(Product 5) Version 3.0 of OW21 Dashboard	Scheduled: Q2 - 2013 Completed:
(Product 5) Version 4.0 of OW21 Dashboard	Scheduled: Q4 - 2013 Completed:
(Product 6) Prototype version 1.0 of TSCA21 Dashboard	Scheduled: Q2 - 2012 Completed:
(Product 6) Version 2.0 of TSCA21 Dashboard	Scheduled: Q4 - 2012 Completed:
(Product 6) Version 3.0 of TSCA21 Dashboard	Scheduled: Q2 - 2013 Completed:
(Product 6) Version 4.0 of TSCA21 Dashboard	Scheduled: Q4 - 2013 Completed:
(Product 7) Prototype version 1.0 of HHRA21 Dashboard	Scheduled: Q2 - 2012 Completed:
(Product 7) Version 2.0 of HHRA21 Dashboard	Scheduled: Q4 - 2012 Completed:
(Product 7) Version 3.0 of HHRA21 Dashboard	Scheduled: Q2 - 2013 Completed:
(Product 7) Version 4.0 of HHRA21 Dashboard	Scheduled: Q4 - 2013 Completed:

Division Approved Yes

CSS

In-Use Tools are Supported and Upgraded

CSS 712 712

Chris Russom
NHEERL
MED

Topic/Theme

7 Dashboards

Project

7.1 Program-Specific Decision Support Tools on Dashboards

Associated Project

None

Task Description

ORD has developed large data repositories that are currently in use across EPA and in the public sector, specifically the ECOTOX, ExpoCastDB, MetaPath, ToxRefDB, ToxCastDB, and ACToR databases. These tools have a diverse client-base and support a wide range of Agency regulatory requirements (e.g., CWA, FIFRA, CERCLA, RCRA). This task will focus on continued maintenance of existing non-CBI data collections and software, and systematic updates of databases to include newly released data that meet QA/QC requirements. These data collections will be critical components of the Dashboard workbench to be developed under 7.2, and to this end the task includes preparation of these applications for seamless integration into the final Dashboards.

Rationale and Research Approach

1. Continued Maintenance of Data Collections: The tools include in this task cover human health and environmental endpoints, measured in environmental media, whole organisms, or in vitro assays. Through the continuous identification, collection, data abstraction, and release of data via publicly accessible websites, the ORD tools will provide a ready source of information on a wide range of chemicals and species for use in risk assessment and in a variety of research activities. Data stewards will have discussions with the Program Offices to identify priorities (e.g., chemicals, species, endpoints, etc) for new data to be included in scheduled updates. 2. Continued Maintenance of Application Infrastructure: In order to maintain the accessibility, security and integrity of each data collection, applications must adhere to Agency IT policies related to application development and web protocols and procedures. 3. Readying Applications for Inclusion in Dashboards: As critical components of the Dashboard workbench, to be developed under Project 7.2, each data steward will be responsible for assisting in preparing their data collection for use within the CSS Dashboards. This process will include identifying when data are ready for release to clients, and possible restrictions to data included in the dashboards (e.g., quality of test design). Data stewards will work with collaborators under 7.2 to ensure systematic updates of data following EPA policies and procedures as outlined by the Office of Environmental Information, maintaining the accessibility, security and integrity of the data. This will be especially important if the data are not linked directly to the original data collection from the Dashboard. Discussions with the Program Offices will be undertaken to ensure a clear understanding of objectives related to the data need exist. 4. Develop Cross-Linkages Between Databases: As large amounts of data are generated via high throughput (HTS) testing techniques (e.g., ToxCast), comprehensive, and high quality in vivo databases will be needed in order to ground truth the in vitro test results. Currently signatures of chemical toxicity linking mammalian in vivo test data (e.g., ToxRefDB) to ToxCast HTS results have been developed, but there is a need to expand these types of approaches to include ecologically relevant test species (i.e., ECOTOX). Therefore, building linkages across the various databases will be an important component of this task.

Outputs from Projects related to this task

Tools in-use are supported by ORD (maintained, upgraded, populated with legacy data) as needed.

Expected Products

(1) Continued maintenance, upgrade and inclusion of in-use tools and databases for screening and prioritization applications (ToxRefDB, ACToR, ToxCastDB, ExpoCastDB)

Type: DATA
DATABASE

Delivery Date (FY): 2016

(2) Continued maintenance, upgrades of in-use tools for human and ecological health effects (e.g., MetaPath, ECOTOX)

Type: DATA
SOFTWARE

Delivery Date (FY): 2016

(3) ToxRefDB, ACToR, ToxCastDB and ExpoCastDB integrated in Knowledge Management infrastructure.

Type: DATA
SOFTWARE

Delivery Date (FY): 2016

(4) Continued maintenance, upgrades and inclusion of in-use tools for human and ecological health effects (e.g., MetaPath, ECOTOX)

Type: DATA
SOFTWARE

Delivery Date (FY): 2016

Start Date Q1 2012

End Date Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NCCT: Richard Judson, Matt Martin, Sumit Gangwal NHEERL: Chris Russom, MED NERL: Jack Jones (Athens)

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) ACToR: Add new data sets including integration of DSSTox and PubChem	Scheduled: Q4 - 2012 Completed:
(Product 1) ExpoCastDB: Add new data sets and automate data loads	Scheduled: Q4 - 2012 Completed:
(Product 1) ToxCastDB: complete redesign and rebuild of system to manage Phase II, Tox21, PubChem and toxicity pathway and MOA data	Scheduled: Q4 - 2012 Completed:
(Product 1) Annual updates	Scheduled: Q4 - 2013 Completed:
(Product 1) Annual updates	Scheduled: Q4 - 2014 Completed:

(Product 2) ECOTOX: Release of pesticide data to public website for litigation and registration review chemicals completed in FY12-Q1&Q2/Q3	Scheduled: Q4 - 2012 Completed:
(Product 2) MetaPath: Add new rat metabolism, and livestock and plant residue information from EPA legacy data	Scheduled: Q4 - 2012 Completed:
(Product 3) Integrate ACToR, ToxCastDB into Data Management Warehouse	Scheduled: Q2 - 2012 Completed:
(Product 3) Integrate ExpoCastDB into Data Management Warehouse	Scheduled: Q4 - 2012 Completed:

Division Approved Yes

CSS Pilot Focused on Delivery of Knowledge Management Infrastructure for Ecological Risk Assessment

CSS 713 713

Tom Purucker
NERL
ERD

Topic/Theme

7 Dashboards

Project

7.1 Program-Specific Decision Support Tools on Dashboards

Associated Project

None

Task Description

This task addresses to Environmental Fate and Effects Division (EFED) need for integrating and automating estimated exposure and effects on species under FIFRA and the Endangered Species Act. OCSPP currently uses a tiered approach for terrestrial and aquatic ecological assessment that uses a diverse library of models. These models are implemented in different programming languages and have disparate user interfaces. EFED has outlined software requirements for integrating these models in a video-conference in July, 2011. The product of this activity is a desktop application and batch execution tool that streamline this workflow by addressing these requirements. Although this pilot focuses on pesticides, we believe that the framework can also be customized for ecological assessment of other environmental chemicals.

Rationale and Research Approach

The primary requirements for integrating include: (a) extracting label information for pesticide formulation labels, (b) interactive/batch exposure modeling runs, (c) overlay geographical areas of expected effects with locations of listed species, (d) real time exploration of the impacts of localized use modifications on listed species effects determinations, (e) preserves a record of use modifications in a way that existing Endangered Species Protection Program tools can make enforceable on the label. We will address these requirements by automating the following tasks: access to use site information from Office of Pesticide Programs Information Network (OPPIN); standardize the assignment of pesticide uses to geographical areas; extract use information from OPP product summary; and develop a database relating zones of concern to listed species to determine biological effects. EFED uses a range of models to estimate ecological exposure scenarios due to pesticide use. For terrestrial species, PRZM, AgDisp (or AgDrift), TerrPlant, T-Rex, T-Herps, Dust, SIP and STIR, provide exposure concentrations at a defined level of geographical resolution with limited physical chemical properties. Similarly, aquatic exposures are estimated using a variety of tools including: EXAMS (linked to PRZM) for concentrations in agricultural farm ponds; KABAM (linked to EXAMS) to estimate exposures for piscivorous species; a modified version of PRZM for estimating downstream exposures; Rice/PFAM for rice paddies; SWAMP for fish and aquatic invertebrates for water bodies that are adjacent to treated fields. Considering the complexity of chemical transport processes, it is infeasible to exhaustively evaluate effects of applying pesticide formulation to crop types across geographical areas on listed species. To address this issue we will develop: (a) an interactive graphical interface for EFED users to evaluate effects due to specific scenarios, and (b) a batch execution tool that automatically evaluates a large array of possible assessment combinations. The former approach will allow for EFED personnel to run model ensembles in response to specific pesticide formulations for identified areas and receptors, while the latter approach has more automation capability to run and document batch runs. Importantly, both approaches will have a common database structure for model inputs and model outputs. In the short term, ERD will develop an integrated user interface that will initially implement the terrestrial suite of models. This will be followed by integration of the aquatic model. This is primarily due to the lower spatial complexity and uncertainty in terrestrial model parameters. A Windows graphical user interface (GUI) will be

developed to simplify selection of model parameters, model execution, and access archived model parameters/results. A relational database will be developed to store the input and output data from the execution of the terrestrial and aquatic models. We will also develop a python library to provide a seamless programming interface to the terrestrial and aquatic models, and the database. This will allow us to evaluate ecological risk assessment on a large-scale using the ORD high-performance computing (HPC) resources, and enable integration of ecological risk assessment models into Dashboard.

Outputs from Projects related to this task

New agreed upon tools are completed and delivered.

Expected Products

(1) Prototype dashboard for OPP to support ecological risk assessment (EPA & contractor)

Type: DATA SOFTWARE

Delivery Date (FY): 2012

(2) Expansion and update of OPP decision support tool to include additional modeling issues identified in 2010 OCSPP/ORD workshop. Includes modification to existing models and new algorithms for chemical fate, transport, and exposure/effect processes.

Type: DATA SOFTWARE

Delivery Date (FY): 2015

Start Date Q1 2012

End Date Q4 2015

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)	**External Collaborators (known or proposed)**
NHEERL: Raimondo (consultation on biological database development) NERL: Purucker, Bohrmann, Parmar	TBD

Milestones

(Product 1) OPP EFED Dashboard Prototype v1.0	Scheduled: Q4 - 2012 Completed:
(Product 1) OPP EFED Dashboard v2.0	Scheduled: Q4 - 2015 Completed:

Division Approved Yes

CSS

Process for Design and Delivery of Program-Specific Decision Support Tools

CSS 711 711

Pat Schmieder
NHEERL
MED

Topic/Theme

7 Dashboards

Project

7.1 Program-Specific Decision Support Tools on Dashboards

Associated Project

None

Task Description

A process is needed for efficient development and delivery of dashboards and decision support tools to EPA Program Offices and Regions. This activity involves collaboration with the Programs and Regions to identify and integrate CSS products into their workflow where appropriate, providing technical guidance and scientific expertise where requested, and on-going communication to identify and reduce information gaps and uncertainties in use of existing and new tools through appropriate targeted research and continued technical support. The development of dashboards will include meetings and surveys to gather information about the bottlenecks in existing Program Office and Region workflows in order to define the requirements for the development of new tools, or the customization of existing tools. Program-specific dashboards will provide one-stopaccess to not only the tools and models needed, but can also serve as a place to access all the supporting information that often represents years of scientific research accomplishments (user manuals, How-To guides, model documentation, technical support documents, QA/QC documentation, issue papers, key related scientific articles), as well as provide contact information for a specific ORD expert available for consultation. ORD will work with the Program Offices and Regions to develop a process that, when fully implemented, will demonstrate ORDs commitment not only to development of state-of- the-science research outputs, but the delivery of those outputs as functional products to the Programs and Regions.

Rationale and Research Approach

The ORD Dashboard Team (PALs & Task Leads across Project 1 & 2) will work with the OCSPP CSS Implementation and Coordination Team , appropriate OW and Regional contacts to address the following near, intermediate and long-term goals: a) develop an efficient process to gather requirements from Program Offices and Regions for specific decision support tools including, models, databases, knowledgebases needed to ensure that the products delivered meet the Program needs, and will continued to be supported as required; b) prioritize the dashboard development based on end-user requirements, tool readiness, scientific guidance and support for the use of the tool, and regulatory acceptance of the tool in the decision making process; c) achieve efficiencies in selecting information integration options and information serving options (i.e., on dashboards, as appropriate) by demonstrating how a series of tools and models can be integrated through a well-chosen and high-need pilot project; d) ensure continued integration of products from all 8 CSS topic areas (that address Program needs described, for example, in EDSP21; OPP21; TSCA21; OW21; ORDs Nov 2010 Research Action Plan for OCSPP Ecological Risk Assessments; NexGen; etc) by integrating new tools, models, datasets, databases, knowledgebases, etc into existing or new Program-specific dashboard as appropriate. We will also communicate with OSWER and the Childrens Health Office to gauge their interest in participating in Dashboard development activities.

Outputs from Projects related to this task

Process used to continue development and delivery of Decision Support Tools.

Expected Products

(1) Results of survey of Program Office/Region requirements for databases / decision support tools.
Type: UNPUBLISHED REPORT Delivery Date (FY): 2012

(2) Standardized process for identifying, prioritizing and implementing decision support tools.
Type: OTHER Delivery Date (FY): 2013

Start Date Q1 2012 **End Date** Q4 2014 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NCCT: I. Shah, R. Judson, D. Reif, Matt Martin, Monica Linnenbrink NHEERL: C. Russom, NERL: J. Jones, T. Purucker

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Initiate interactions between ORD Dashboard Team and the OCSPP CSS Implementation and Coordination Team to begin the process of defining needs for tools, models, databases, knowledgebases.	Scheduled: Q1 - 2012 Completed:
(Product 1) Initiate interactions between ORD Dashboard Team and appropriate OW and Regional by identifying user groups and targeting surveys to better understand in use tools/models, tools in development, and needs for tools and expertise for the future.	Scheduled: Q3 - 2012 Completed:
(Product 1) Survey OCSPP to better understand requirements (e.g., models, tools, technical expertise needed to improve workflow); Surveys will build off of currently available information (e.g., CREM inventory; ORDs Nov 2010 Research Action Plan for OCSPP Ecological Risk Assessments, etc) and will be targeted at appropriate level (Division, Branch, Technical Team, etc) as the OCSPP CSS Implementation and Coordination Team advises; Interpretation of survey results and follow-up actions will be jointly decided by the ORD and the OCSPP CSS Implementation and Coordination Team.	Scheduled: Q3 - 2012 Completed:
(Product 1) Survey OW and Regions at appropriate level to better understand their requirements for models, tools, technical expertise, etc as described above.	Scheduled: Q4 - 2012 Completed:
(Product 2) ORD staff monitor work flow of Program Offices and Regions in order to understand needs and tools most used to incorporate into Dashboards.	Scheduled: Q2 - 2012 Completed:
(Product 2) User group sessions with Program Offices and Regions to demo prototypes of dashboards and solicit feedback for enhancement to better meet their needs. Incorporate feedback into prototypes.	Scheduled: Q4 - 2012 Completed:
(Product 2) Workshops with Program Offices and Regions to demonstrate how to use dashboards. Continually enhance dashboards to meet their needs.	Scheduled: Q1 - 2013 Completed:
(Product 2) Dashboard Team and OCSPP CSS Implementation and Coordination Team work together to assess the success of the initial deployment of Program	Scheduled: Q4 - 2013

Specific Dashboards (EDSP21, TSCA21, etc.) to improve the deployment and use of tools and models by OCSPP. (A similar process will be used as each dashboard is employed).	Completed:
(Product 2) ORD Dashboard Team (working with MIs, PALs and Task Leads across CSS to facilitate interaction with Program Offices teams) will work with OCSPP CSS Implementation and Coordination Team, OW, and Regional teams to continue to identify additional needs for development, deployment, and maintenance of tools, models, databases, knowledgebases, and ORD technical expertise from all 8 CSS Topic Areas.	Scheduled: Q4 - 2016 Completed:

Division Approved Yes

CSS

Dashboard Workbench

CSS 723 723

Richard Judson
NCCT
IO

Topic/Theme

7 Dashboards

Project

7.2 Knowledge Management and Decision Support Tools

Associated Project

None

Task Description

A workbench will be developed to provide user-friendly modular interfaces or widgets (for web or mobile apps) to display data results from databases or predictive tools that can be used in decision-making. Dashboard developers will use this toolkit to construct individual modular dashboards that can be integrated into desired workflows. Publicly available open-source toolkits are available (such as BIRT, bioclipse, taverna, and KNIME workflow managers, for which appropriate extensions can be built) and these will be evaluated before any custom toolkit development would be considered.

Rationale and Research Approach

1. Inventory publicly available toolkits for constructing dashboard. This will include toolkits designed for building web-based and mobile app applications. We will deliver a report on available toolkits including strengths and weakness and overall functionality. 2. Evaluate needs of envisioned dashboards against functionality provided by public open-source toolkits: This will require working with designers of the dashboards (Task 7.1) to define needs for at least the first round of dashboards. We will deliver a report comparing needs against functionality and a decision on how to proceed. If we believe that a publicly available, open source toolkit will meet the needs of at least year 1 dashboards, that will be selected and step #3 below will not be worked on. 3. Toolkit design if needed: if the public toolkits do not meet the needs of the dashboards, start design and construction of in-house toolkit. This will involve design and coding of widgets, and coding to interface widgets with web services. 4. Delivery of toolkit and how-to documentation: This will include a package of software tool that developers can use, in addition to required documentation for dashboard designers to start work. 5. Develop widgets for specific databases and tools currently in place or being developed as part of the other CSS projects. Even if we start with a public, open source toolkit, there will likely be specific, required widgets not available. For these, we will develop custom code that can interface with the selected toolkit.

Outputs from Projects related to this task

(1) Software wrappers providing standardized queries and Project 7.1. Products (databases / knowledge-bases) (2) Generic software widget library for tables, graphs, workflows, etc. (3) Software toolkit for building dashboards and workbenches (4) Specialized software widgets including those developed by EPA or external collaborators (5) Updates for software wrappers, widgets, toolkits

Expected Products

(1) Software wrappers providing standardized queries and Project 7.1. Products (databases / knowledge-bases)

Type: DATA SOFTWARE — Delivery Date (FY): 2012

(2) Generic software widget library for tables, graphs, workflows, etc.

Type: DATA — Delivery Date (FY): 2012

SOFTWARE

(3) Software toolkit for building dashboards and workbenches
Type: DATA SOFTWARE
Delivery Date (FY): 2012

(4) Specialized software widgets including those developed by EPA or external collaborators
Type: DATA SOFTWARE
Delivery Date (FY): 2016

(5) Updates for software wrappers,widgets, toolkits
Type: DATA SOFTWARE
Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)
NCCT: Shah, Reif, Martin NHEERL: ???

External Collaborators (known or proposed)
TBD

Milestones

(Product 1) Prototype Version 1.0 of Webservices for Dashboard DB & KB	Scheduled: Q3 - 2012 Completed:
(Product 1) Version 2.0 of Webservices for Dashboard DB & KB	Scheduled: Q4 - 2012 Completed:
(Product 1) Version 3.0 of Webservices for Dashboard DB & KB	Scheduled: Q1 - 2013 Completed:
(Product 1) Version 4.0 of Webservices for Dashboard DB & KB	Scheduled: Q1 - 2014 Completed:
(Product 2) Prototype Version 1.0 of Widget library for Dashboards	Scheduled: Q2 - 2012 Completed:
(Product 2) Version 2.0 of Widget library for Dashboards	Scheduled: Q4 - 2012 Completed:
(Product 2) Version 3.0 of Widget library for Dashboards	Scheduled: Q1 - 2013 Completed:
(Product 2) Version 4.0 of Widget library for Dashboards	Scheduled: Q1 - 2014 Completed:
(Product 3) Prototype Version 1.0 of Widget library for Dashboards	Scheduled: Q2 - 2012 Completed:
(Product 3) Version 2.0 of Widget library for Dashboards	Scheduled: Q4 - 2012 Completed:

(Product 3) Version 3.0 of Widget library for Dashboards	Scheduled: Q1 - 2013 Completed:
(Product 3) Version 4.0 of Widget library for Dashboards	Scheduled: Q1 - 2014 Completed:
(Product 4) Version 1.0 of specialized widget library	Scheduled: Q1 - 2013 Completed:
(Product 4) Version 2.0 of specialized widget library	Scheduled: Q1 - 2014 Completed:

Division Approved Yes

CSS Data Management Warehouse

CSS 721 721

David Reif
NCCT
IO

Topic/Theme

7 Dashboards

Project

7.2 Knowledge Management and Decision Support Tools

Associated Project

None

Task Description

Existing data management systems will be inventoried to federate raw data generated by CSS/EPA and available in the public domain on: chemical structure, production, environmental fate, human use, ecological and health effects, exposure, etc. Much of this infrastructure exists in EPA databases but requires continuous maintenance. (Among other things, maintenance includes continually adding new data to existing databases and carrying out appropriate data QC. Therefore at the stage of allocating resources, thought needs to be given to this ongoing support that will be required.) This task will result in the design and construction of the database backend and data serving machinery to provide data to the dashboards. It is anticipated that this work will be carried out by a combination of ORD staff and contractors.

Rationale and Research Approach

1. Inventory of data sources: Current large repositories of data include ECOTOX, MetaPath, ACToR, ToxRefDB, ToxCastDB, ExpoCastDB, the WikiLIMS project of NHEERL, the Virtual Tissue Knowledgebase (VTKB), DSSTox and HERO. These include access to hazard, exposure and use data available in the public domain, as well as data from EPA studies and guideline registrant data. (Technically, it is feasible to create parallel systems for public and public plus CBI data so that internal decision-makers can have secure access to all of the data they currently use in a dashboard-enabled manner.) Data quality is an issue with all data sources, but we envision that this will be handled at the data source level, and handled in the same way it is currently done for resources being used by the program offices. We will produce and inventory of information resources from ORD, EPA-wide and external. 2. Investigate information integration options: All of these data currently exist in a set of databases, although using different systems (Oracle, MySQL, MS ACCESS and Semantic MediaWiki). In order to have a federated system that can allow any data to be accessed by any dashboard, we need to either consolidate in one database system or to write smart wrappers around each of the individual systems. We will evaluate technical options to integrate data into a single system (probably by mirroring the original data sources to allow for easy updates) vs. writing smart wrappers around each data source. This will include technical, programmatic and financial considerations. The pilot project under Dashboard Project 1 will serve as an initial opportunity investigate and evaluate a specific approach to integrating models and at the same time meeting a critical Program Office need. 3. Investigate information serving technology: The state-of-the-art technology for building a flexible data-view system uses web services. In this system, a user (in this case through a dashboard) issues a request for information via a URL. A web services program running on a server interprets this, goes to the required databases or models, and then returns the requested information in an appropriate format. Common formats are XML and MS Excel. With XML, the dashboard software would know how to convert this information into a web page, or a view for a smart phone app. For financial or other reasons (e.g., having to do with contract mechanisms for certain EPA databases) it might be infeasible to directly build web services into certain databases, so a wrapper program that mimics a web service component might need to be built. There are competing web services technologies that will have to be evaluated. We will produce a proposal for how the web services will be implemented for all selected

databases. The pilot project under Dashboard Project 1 will be explored as an opportunity to investigate and evaluate a specific approach to integrating models and at the same time meeting a critical Program Office need. 4. Construction of the backend data warehouse / virtual knowledgebase: Once the system has been designed, we will construct the warehouse and the appropriate web services. Much of the data infrastructure is already in place, so the main effort will go into designing and building the web services and wrappers. We will produce working database-web services system for the initial databases. (FY2 Q2 with additional databases added at 6 month intervals)

Outputs from Projects related to this task

(1) A collection of databases and tools for use by decision-makers (2) Ontologies that help describe and organize the information (3) Web services that allow flexible queries into the knowledgebases (4) A suite of tools to construct dashboards or workflows.

Expected Products

(1) Relational Databases and RDF Knowledge-bases with effects and exposure information needed by the products of Project 7.1. Products.

Type: DATA DATABASE

Delivery Date (FY): 2012

(2) Continued integration of databases into Knowledge Management infrastructure.

Type: DATA DATABASE

Delivery Date (FY): 2016

Start Date Q1 2012

End Date Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

NCCT: Judson, Reif, Martin, Shah, Gangwal
NHEERL: Russom, Schmieder NERL: Croghan

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Survey of databases and knowledgebases required for decision support systems	Scheduled: Q3 - 2012 Completed:
(Product 1) Design of Webs service infrastructure	Scheduled: Q3 - 2012 Completed:
(Product 1) V1 of VDKW	Scheduled: Q3 - 2012 Completed:
(Product 1) V2 of VDKW	Scheduled: Q1 - 2013 Completed:
(Product 1) V3 of VDKW	Scheduled: Q3 - 2013 Completed:

(Product 1) V4 of VDKW	Scheduled: Q1 - 2014 Completed:
(Product 1) Quarterly updates of VDKW (ongoing)	Scheduled: Q4 - 2016 Completed:

Division Approved Yes

CSS

Decision Analysis Tools

CSS 724 724

Richard Judson
NCCT
IO

Topic/Theme

7 Dashboards

Project

7.2 Knowledge Management and Decision Support Tools

Associated Project

None

Task Description

Existing and new computational decision analysis tools or models will be incorporated into the framework to assist decision making. We anticipate that these tools will primarily be publicly accessible / available as opposed to commercial packages. These will include statistical and machine learning tools, probabilistic risk assessment tools, Monte Carlo simulations, etc. Open source backend computational tools will be used, such as those available in R and Java. Where possible, bridging the various data streams and tools may be streamlined with an open-source workflow manager as well. These decision analysis tools will explicitly provide metrics for underlying data quality and model uncertainty to the user. This task will provide methods to integrate these tools into dashboards, typically by providing a wrapper that will fit into the web services framework being designed to manage data queries.

Rationale and Research Approach

1. Define needed tools: This will be in collaboration with dashboard designers and users. The initial delivery will be a prioritized inventory of tools need by dashboards, including descriptions of inputs and outputs, operating systems requirements, typical run times, availability of source code, proprietary use restrictions, and typical use cases. 2. Construction of generic web services support for tools: We will build a generic wrapper toolkit that will act as a web service to access tools or models. The input will be a URL which will be passed to a web server, which will in turn pass need parameters to the model; parse the output and return the results in one of the standard formats. 3. Construction of required wrappers and web services: For each tool we will construct a specific wrapper that will fit into the tool web service framework. 4. The NHEERL data management system (WikiLiMS) provides enhanced usability and automated work flows to handle Illumina Microarray and Sequencing data being generated in the NHEERL Research Core Unit. Improvements to this systems are necessary for better access to raw data generated within the laboratory supporting enhanced meta-analysis of high content data generated in different studies as well as providing additional data not captured in the published report for risk assessors throughout the Agency. 5. Support integrated data flow and analysis across the Agency including models, databases, and other computational tools covering the continuum from global exposures to genome-level health effects. This analysis will gather user requirements for the system, identify institutional implementation issues, and survey highlights of considerations and constraints to serve as a basis for future deployment. It is anticipated that such a document will help to organize the targeted efforts within the individual ITRs to provide greater interoperability moving forward.

Outputs from Projects related to this task

(1) Software libraries to integrate decision support tools needed by the Project 7.1. Products are created outside of Dashboards; (2) Updates to software libraries for integrating decision support tools needed by the Project 7.1. products.

Expected Products

(4) A systems design description (SDD) for a platform to support integrated data flow and analysis across the Agency including models, databases, and other computational tools covering the continuum from global exposures to genome-level health effects. This document will provide user requirements for the system, identify institutional implementation issues, and survey highlights of considerations and constraints to serve as a basis for future deployment. It is anticipated that such a document will help to organize the targeted efforts within the individual ITRs to provide greater interoperability moving forward.

Type: OTHER Delivery Date (FY): 2012

(3) WikiLIMS 2.0 release: This latest release of the NHEERL data management system will provide enhanced usability and automated work flows to handle Illumina Microarray and Sequencing data being generated in the NHEERL Research Core Unit. This system provides better access to raw data generated within the laboratory supporting enhanced meta-analysis of high content data generated in different studies as well as providing additional data not captured in the published report for risk assessors throughout the Agency.

Type: OTHER Delivery Date (FY): 2012

(1) Software libraries to integrate decision support tools needed by the Project 7.1. Products are created outside of Dashboards

Type: DATA SOFTWARE Delivery Date (FY): 2013

(2) Updates to software libraries for integrating decision support tools needed by the Project 7.1. products.

Type: DATA SOFTWARE Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)	**External Collaborators (known or proposed)**
NCCT: Shah, Reif, Martin NHEERL: ??? NERL: J. Jones	TBD

Milestones

(Product 1) Version 1.0 of software libraries and webservices for external decision support tools	Scheduled: Q1 - 2013 Completed:
(Product 1) Version 2.0 of software libraries and webservices for external decision support tools	Scheduled: Q1 - 2014 Completed:
(Product 2) Version 2.0 of WikiLIMS	Scheduled: Q3 - 2012 Completed:
(Product 2) Systems design description (SDD) document	Scheduled: Q4 -

2012
Completed:

Division Approved Yes

CSS

Ontologies for Interoperability

CSS 722 722

Imran Shah
NCCT
IO

Topic/Theme

7 Dashboards

Project

7.2 Knowledge Management and Decision Support Tools

Associated Project

None

Task Description

The objective of the activity is to deliver tools that organize evidence about chemical effects across levels of biological organization so that it can be used efficiently in different Dashboard tools. This information is currently stored using unstructured text, or relational schemas in internal databases (e.g. ToxRefDB, ToxCast, DSSToX) and external resources (e.g. CTD, PubMed, etc.). As most of these resources use differing data models and terminologies, standardizing this information is necessary to synthesize diverse types of chemical effects. In addition, since knowledge of the pathways involved in toxicity is incomplete, it is important to relate chemical effects to other public information resources in order to elucidate their mechanistic linkages with physiological processes. The products of this activity provides a flexible knowledge-based framework that will formally encode information about chemicals, toxic effects and potential intervening pathways.

Rationale and Research Approach

A collaborative approach will be used to engage stakeholders from EPA and ongoing external US/international efforts. 1. Ontology development: The ontology will be developed using available knowledge representation schemes in biology and domain knowledge in toxicology. The mode of action (MOA) framework for evaluating human relevance will be considered a specific use-case for defining the scope of the ontology. The key steps include: (a) identification of key toxicology concepts and public domain referential terminologies that can be used to standardize them (e.g. chemicals, genes, proteins, cells, anatomic locations, cellular functions, histological lesions, diseases, etc.), (b) standardizing key relationships between these concepts using public relational terminologies, and (c) developing an Ontology Web Language (OWL) specification to formally describe and relate chemicals, assays, effects and pathways (semantics). The ontology will be disseminated using a custom widget that can be included in dashboards. 2. Effects - Interoperability: Information about chemicals will be translated into a consistent semantics using the ontology (and terminology standardization). This will enable interoperability between three main sources of information: ToxRefDB, ToxCastDB, and VT-KB. This information will be disseminated as a dashboard widget to search, browse and graphically visualize this information in dashboards. 3. Pathways - Interoperability Normal pathways: Public domain information about biological pathways will be related to effect data in order to analyze possible linkages relevant in the mode of action.

Outputs from Projects related to this task

(1) A collection of databases and tools for use by decision-makers (2) Ontologies that help describe and organize the information (3) Web services that allow flexible queries into the knowledgebases (4) A suite of tools to construct dashboards or workflows.

Expected Products

(1) plan and construct needed ontologies for databases going into the Knowledge Bases.

Type: DATA
DATABASE

Delivery Date (FY): 2012

(2) Quarterly updates and additions to the ontologies
Type: OTHER Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported?
Maybe

Could NCER contribute to this task? Yes

Internal Collaborators (known or proposed)
NCCT: Judson, Reif, Martin, Jack, Knudsen
NHEERL: Stephen Edwards, Chris Corton,

External Collaborators (known or proposed)
TBD

Milestones

(Product 1) Version 1.0 of Terminology for exposure, occurrence, use and effect for dashboards	Scheduled: Q3 - 2012 Completed:
(Product 1) Version 1.0 of Ontology for toxicity pathways (OnToP)	Scheduled: Q3 - 2012 Completed:
(Product 1) Linkage with Exposure Ontology (ExO)	Scheduled: Q4 - 2013 Completed:
(Product 1) Linkage with AOP/Effectopedia	Scheduled: Q4 - 2013 Completed:

Division Approved Yes

CSS

Development of Evaluation & Outreach Team

CSS 812 812

Hisham El-Masri
NHEERL
ISTD

Topic/Theme

8 Evaluation

Project

8.1 Evaluation Research and Development

Associated Project

None

Task Description

CSS research outputs must be evaluated to determine that the methods being produced and the data being generated are reliable, predictive, and have utility if applied to characterize risk of various contexts or to compare risk management alternatives. Thus, the outputs must be evaluated to determine if and how they will best be utilized in risk assessment, risk management, and decision-making by stakeholders such as program and regional offices (Partners). This task will develop qualitative and quantitative measures to assess the utility and performance of CSS and how its research can provide the Partners with tools and methods for risk assessment and management.

Rationale and Research Approach

The overall goal of these tasks is to provide defensibility for the science performed within CSS for use in risk assessment, risk management, and decision making. These tasks will develop approaches for estimating and characterizing the value in technologies and methods used in CSS to help inform their use in risk assessment, risk management, and decision-making, as well as to benchmark the data, methods, and models being developed within CSS. Evaluation of the effectiveness of CSS research begins with developing measurable objectives in coordination with our Partners. To this end, and prior to developing evaluation metrics, an understanding of the Partners needs and aligning them with outputs and products specified by each topic in CSS must be established. This can initially be conducted via obtaining information through pro forma surveys and interviews in an overall outreach plan. The purpose of this plan is to outline the outreach efforts ORD will implement to ensure that ORDs CSS research is meeting the needs of EPA Program Offices and Regions. This plan includes goals, objectives (measures of success), target audiences, outreach approach and strategies, key messages, timeline and evaluation. Communicating the outcomes of the outreach plan to CSS management for further fine-tuning of outputs and products is also a necessary component of the evaluation process. Once surveys are conducted and product usage is established, measurable objectives and evaluation metrics will be developed. After that, the measurable objectives will be reviewed annually to determine if goals are being reached. In view of aligning CSS research with partners needs, evaluation metrics of Utility and Performance measures will be developed. Utility measures are developed for the qualitative evaluation of the responsiveness of CSS research to partnersimmediate, short-term and long-term needs. Performance measures are the quantitative evaluation of the application of data, methods and models as they are generated by CSS research. They may include metrics such as accuracy, precision, sensitivity, and specificity for comparison of data, tools and models with default approaches used by Partners. Comparisons could be done piecemeal,in which specific data/method/model used in an existing approaches is replaced by a new data/method/model. This would result in an evaluation of the incrementalvalue of information benefit of the new data/method/model. Alternatively, the comparison could be made at an integrated level, in which an entirely new approach to the assessment is compared with the existing one. Development and application of Utility and Performance measures and metrics for CSS will require the establishment of teams including subject matter experts and partners (program and regional offices) representatives.

Outputs from Projects related to this task

Overall program performance and success assessment based on understanding of Partnersneeds and how the Partners will benefit from CSS research products.

Expected Products

(1) List of team members with ORD, Program Office and Regional representatives

Type: OTHER Delivery Date (FY): 2012

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

Potential team members include the following: Hisham El-Masri, Lyle Burgoon, Kate Guyton, Monica Linnenbrink, Sue Euling, and selected program and regional offices representatives.

External Collaborators (known or proposed)

TBD

Milestones

Develop evaluation and outreach team Scheduled: Q1 - 2012
Completed:

Division Approved Yes

CSS Development of Evaluation Metrics, Evaluation & Outreach Plan

CSS 811 811

Hisham El-Masri
NHEERL
ISTD

Topic/Theme

8 Evaluation

Project

8.1 Evaluation Research and Development

Associated Project

None

Task Description

CSS research outputs must be evaluated to determine that the methods being produced and the data being generated are reliable, predictive, and have utility if applied to characterize risk of various contexts or to compare risk management alternatives. Thus, the outputs must be evaluated to determine if and how they will best be utilized in risk assessment, risk management, and decision-making by stakeholders such as program and regional offices (Partners). This task will develop qualitative and quantitative measures to assess the utility and performance of CSS and how its research can provide the Partners with tools and methods for risk assessment and management.

Rationale and Research Approach

The overall goal of these tasks is to provide defensibility for the science performed within CSS for use in risk assessment, risk management, and decision making. These tasks will develop approaches for estimating and characterizing the value in technologies and methods used in CSS to help inform their use in risk assessment, risk management, and decision-making, as well as to benchmark the data, methods, and models being developed within CSS. Evaluation of the effectiveness of CSS research begins with developing measurable objectives in coordination with our Partners. To this end, and prior to developing evaluation metrics, an understanding of the Partners needs and aligning them with outputs and products specified by each topic in CSS must be established. This can initially be conducted via obtaining information through pro forma surveys and interviews in an overall outreach plan. The purpose of this plan is to outline the outreach efforts ORD will implement to ensure that ORDs CSS research is meeting the needs of EPA Program Offices and Regions. This plan includes goals, objectives (measures of success), target audiences, outreach approach and strategies, key messages, timeline and evaluation. Communicating the outcomes of the outreach plan to CSS management for further fine-tuning of outputs and products is also a necessary component of the evaluation process. Once surveys are conducted and product usage is established, measurable objectives and evaluation metrics will be developed. After that, the measurable objectives will be reviewed annually to determine if goals are being reached. In view of aligning CSS research with partners needs, evaluation metrics of Utility and Performance measures will be developed. Utility measures are developed for the qualitative evaluation of the responsiveness of CSS research to partnersimmediate, short-term and long-term needs. Performance measures are the quantitative evaluation of the application of data, methods and models as they are generated by CSS research. They may include metrics such as accuracy, precision, sensitivity, and specificity for comparison of data, tools and models with default approaches used by Partners. Comparisons could be done piecemeal,in which specific data/method/model used in an existing approaches is replaced by a new data/method/model. This would result in an evaluation of the incrementalvalue of information benefit of the new data/method/model. Alternatively, the comparison could be made at an integrated level, in which an entirely new approach to the assessment is compared with the existing one. Development and application of Utility and Performance measures and metrics for CSS will require the establishment of teams including subject matter experts and partners (program and regional offices) representatives.

Outputs from Projects related to this task

Overall program performance and success assessment based on understanding of Partners needs and how the Partners will benefit from CSS research products.

Expected Products

(1) Understanding of client needs, and how they will measure product utility; information obtained through pro forma surveys and interviews.

Type: OTHER Delivery Date (FY): 2012

(2) Metrics based on client needs and proposed client utility measures that will be applied by CSS Evaluation Teams

Type: OTHER Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016 **Cross Research Project Output Supported?** Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

Potential team members include the following: Lyle Burgoon, Kate Guyton, Monica Linnenbrink, Sue Euling, and selected program and regional offices representatives.

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Development of performance measures for the technical quantitative evaluation of the accuracy, sensitivity, and specificity of CSS data, methods and models in comparison to default approaches used by partners and stakeholders.	Scheduled: Q1 - 2013 Completed:
(Product 1) Assessment of CSS research structure for the integration of individual projectsproducts and outputs to answer current and emergent needs of partners and stakeholders	Scheduled: Q3 - 2012 Completed:
(Product 2) Draft Program Office and Regional Evaluation, Outreach and Engagement Plan	Scheduled: Q1 - 2012 Completed:
(Product 2) Interviews with ORD, Program Office and Regions to get input on plan and incorporate feedback into plan	Scheduled: Q1 - 2012 Completed:
(Product 3) Interviews with ORD, Program Office and Regions to get input on plan and incorporate feedback into plan	Scheduled: Q2 - 2012 Completed:
(Product 3) Draft External Stakeholder Outreach and Engagement Plan	Scheduled: Q1 - 2012 Completed:
(Product 4) Gather baseline information through survey tool for Program Office and Regions awareness, understanding and usage of CSS and products	Scheduled: Q2 - 2012 Completed:

(Product 4) Gather baseline information through survey tool for External Stakeholder awareness, understanding and usage of CSS and products

Scheduled: Q3 - 2012

Completed:

Division Approved Yes

CSS

Development of Evaluation Plan

CSS 821 821

Kate Guyton
NCEA
NCEA-WASH

Topic/Theme

8 Evaluation

Project

8.2 Evaluation Research Translation

Associated Project

None

Task Description

Evaluation research focuses on understanding the utility of CSS data, methods and models in risk assessment and risk management. This will include evaluating the reliability, uncertainty and impacts of these approaches, and the value of the information generated. The research described in this theme is an internal process of evaluation; it is not intended to replace or supersede external, peer-driven evaluations such as SAB/SAPs or BOSC panels. Specifically, Task 8.2.1 will focus on developing an evaluation plan. This will include engagement with EPA users of the products of CSS research, to ensure that the products meet the needs of EPA Offices in making policy and regulatory decisions. Additionally, it will perform internal evaluation by applying CSS utility evaluation criteria and metrics. The Advancing the Next Generation of Risk Assessment (NexGen Risk Assessment) Program, an EPA-led, interagency program that advances the science of risk assessment, is a key feature of Task 8.2.1. The NexGen Risk Assessment program will perform realistic case studies to evaluate CSS products that incorporate CSS utility evaluation criteria and metrics, while developing best practices for the use of CSS data in science and risk assessments. Task 8.2.2 will address longer-term objectives, including applying value of information analyses. Task 8.2.3 will identify and communicate CSS Program improvement practices. In all, the effort will focus on evaluating the outputs from other CSS Themes to determine if and how they will best be utilized in multiple types of EPA assessments (e.g., human health, exposure, ecological, life-cycle, etc), risk management, and decision-making. As such, the evaluation is focused on discerning the role of CSS products in informing current or future decision-making of the Agency. Evaluation will identify overarching challenges for the CSS program that can be addressed through future enhancements and developments. Thus, an important aspect of evaluation is that the task outputs from this topic will feed back into other CSS topics.

Rationale and Research Approach

A challenge for evaluation is that CSS products are intended to inform a diversity of EPA assessments and decisions regarding chemical safety and sustainability, made by multiple EPA Offices and programs. Accordingly, this Task will establish a process for regular engagement with CSS partners and teams during product development. As emphasized in a number of EPA risk assessment documents (U.S. EPA, 1998 [Guidelines for Ecological Risk Assessment], U.S. EPA, 2003 [Framework for Cumulative Risk Assessment], U.S. EPA, 2006 [Framework for Assessing Health Risk of Environmental Exposures to Children]) and the recent NRC Science and Decisions report (NRC, 2009), a key aspect of problem formulation is the fit for purpose design of the assessment. For example, in human health or ecological risk assessment, the data, methods, and analysis used to characterize exposures and effects should be designed to evaluate the available risk management options. Therefore, a key aspect of this task is an evaluation of the ability of CSS products to enhance reliability and reduce uncertainty (e.g., in data collection, generation, interpretation, and analysis) in discriminating among options in risk assessment and management. In addition, recognizing the iterative nature of the assessment process, it will also focus on the identification of additional data or analysis needs that would better inform either the current or a future decision. A separate part of this

Task is an internal evaluation of CSS by applying utility evaluation criteria and metrics. The NexGen Risk Assessment Program will perform evaluation of CSS products by applying these criteria and metrics as part of NexGen Risk Assessment case study development. Cases are envisioned to address both broad-themed exploratory efforts as well as more specific issues. These will include human health risk assessments using CSS data, methods and models, to advance prioritization among chemicals for testing and assessment, and to perform risk assessments supporting decision-making for chemicals and chemical groups. Chemical case studies will be grouped based on the available data from CSS using NexGen Risk Assessments current three tier system, where Tier I assessments have the largest amount of uncertainty, and Tier III assessments have the least amount of uncertainty. By combining the current NexGen Risk Assessment case study framework with utility evaluation criteria and metrics from our Partners, we will be able to drive forward the integration of molecular, systems biology, and high throughput screening data into the practice of risk assessment, while also evaluating the utility of CSS Products. For instance, CSS developed high throughput screening data about a chemical would be evaluated through a NexGen Risk Assessment Tier I case study, with specific attention paid to our Partnersutility criteria and metrics. By using the NexGen case study approach, in concert with the utility criteria and metrics, we can not only evaluate the CSS Product for fitness for use, but we can also begin to work with the Partner to identify ways to incorporate this product into a science or risk assessment product. In addition, Comprehensive Environmental Analysis (CEA) will be used in select situations in collaboration with the NexGen Risk Assessment approach. Comprehensive Environmental Analysis goes beyond consideration of a products life cycle. CEA builds upon the life cycle analysis (LCA) to encompass environmental fate and transport through media, exposure-dose characterization, ecological and health impacts, as well as direct and indirect effects of the primary and secondary stressors associated with a chemical. CEA has been demonstrated with nanomaterials in the past; however, we will apply CEA to all classes of chemicals in CSS. CEA will enable us to identify what we know, and also what we do not yet know about a chemical. This will allow us to identify, with help from our Partners, areas for future research within CSS. From an evaluation standpoint, CEA will facilitate our use of utility evaluation criteria and metrics and will complement our NexGen Risk Assessment case studies. For instance, CEA will help us anchor our case studies within specific product, exposure, and health contexts. In addition, by combining NexGen Risk Assessment methods with CEA, we will be able to perform comprehensive evaluations of CSS products, by simultaneously considering utility evaluation criteria and metrics for all parts of the source-to-outcome continuum. In all, this evaluation research will aid the Agency in evaluating the value of CSS information and products for addressing critical decisions, including prioritization of chemical classes and processes for assessment and action, and extrapolation from data-rich to data-poor situations.

Outputs from Projects related to this task

Evaluation of CSS product utility prior to and following product delivery to the Partners; continuing improvement of the CSS Program through feedback from the evaluation process and from Partners.

Expected Products

(1) Regular product feedback sessions with CSS Partners and CSS Teams during product development.

Type: OTHER Delivery Date (FY): 2016

(2) CSS product utility improved by internal application of CSS utility evaluation criteria and metrics, including the use of realistic case studies.

Type: OTHER Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

Potential team members include the following: Hisham El-Masri, Lyle Burgoon, Monica Linnenbrink, Sue Euling, Michael Davis, and selected program and regional offices representatives.

External Collaborators (known or proposed)

TBD

Milestones

None

Division Approved Yes

CSS

Identifying and Communicating CSS Program Improvement Practices

CSS 823 823

Kate Guyton
NCEA
NCEA-WASH

Topic/Theme

8 Evaluation

Project

8.2 Evaluation Research Translation

Associated Project

None

Task Description

Evaluation research focuses on understanding the utility of CSS data, methods and models in risk assessment and risk management. This will include evaluating the reliability, uncertainty and impacts of these approaches, and the value of the information generated. The research described in this theme is an internal process of evaluation; it is not intended to replace or supersede external, peer-driven evaluations such as SAB/SAPs or BOSC panels. Specifically, Task 8.2.1 will focus on developing an evaluation plan. This will include engagement with EPA users of the products of CSS research, to ensure that the products meet the needs of EPA Offices in making policy and regulatory decisions. Additionally, it will perform internal evaluation by applying CSS utility evaluation criteria and metrics. The Advancing the Next Generation of Risk Assessment (NexGen Risk Assessment) Program, an EPA-led, interagency program that advances the science of risk assessment, is a key feature of Task 8.2.1. The NexGen Risk Assessment program will perform realistic case studies to evaluate CSS products that incorporate CSS utility evaluation criteria and metrics, while developing best practices for the use of CSS data in science and risk assessments. Task 8.2.2 will address longer-term objectives, including applying value of information analyses. Task 8.2.3 will identify and communicate CSS Program improvement practices. In all, the effort will focus on evaluating the outputs from other CSS Themes to determine if and how they will best be utilized in multiple types of EPA assessments (e.g., human health, exposure, ecological, life-cycle, etc), risk management, and decision-making. As such, the evaluation is focused on discerning the role of CSS products in informing current or future decision-making of the Agency. Evaluation will identify overarching challenges for the CSS program that can be addressed through future enhancements and developments. Thus, an important aspect of evaluation is that the task outputs from this topic will feed back into other CSS topics.

Rationale and Research Approach

Collaboration with CSS partners is essential for the success of Chemical Safety research. EPA will continue to seek input to ensure Program Offices and Regions can use and benefit from the developed research products. In order to ensure outreach to EPA Program Offices and Regions is effective; baseline measurements must be gathered to determine existing Program Office and Region awareness, interest, usage, satisfaction with and participation in EPAs research. Once baselines are developed, measurable objectives can be developed to assess the effectiveness of ORDs outreach to Program Offices and Regions as well as support of research products. Below is a listing of how baselines will be developed: (1) Program Office and Region surveys to determine existing awareness, interest, support, usage and satisfaction levels with Chemical Safety research products. (2) Conduct user focus groups to solicit input on development and functionality of research products and tools. Specifically focus groups will be used for the development of the CSS Dashboards. (3) Track and analyze usage trends of developed research tools and products. (4) Track and analyze feedback provided about research products. (5) Aligning with the implementation of the CSS Research Action Plan, track and analyze gain in efficiency (number of person-days/hours saved, number of additional chemicals evaluated).

Outputs from Projects related to this task

Evaluation of CSS product utility prior to and following product delivery to the Partners; continuing improvement of the CSS Program through feedback from the evaluation process and from Partners.

Expected Products

(1) CSS Program Improvement Practices identified and potential future impacts quantified

Type: OTHER Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

Potential team members include the following: Hisham El-Masri, Lyle Burgoon, Monica Linnenbrink, Sue Euling, Michael Davis, and selected program and regional offices representatives.

External Collaborators (known or proposed)

TBD

Milestones

None

Division Approved Yes

CSS

Long-term Evaluation of CSS Product Utility by CSS Partners

CSS 822 822

Kate Guyton
NCEA
NCEA-WASH

Topic/Theme

8 Evaluation

Project

8.2 Evaluation Research Translation

Associated Project

None

Task Description

Evaluation research focuses on understanding the utility of CSS data, methods and models in risk assessment and risk management. This will include evaluating the reliability, uncertainty and impacts of these approaches, and the value of the information generated. The research described in this theme is an internal process of evaluation; it is not intended to replace or supersede external, peer-driven evaluations such as SAB/SAPs or BOSC panels. Specifically, Task 8.2.1 will focus on developing an evaluation plan. This will include engagement with EPA users of the products of CSS research, to ensure that the products meet the needs of EPA Offices in making policy and regulatory decisions. Additionally, it will perform internal evaluation by applying CSS utility evaluation criteria and metrics. The Advancing the Next Generation of Risk Assessment (NexGen Risk Assessment) Program, an EPA-led, interagency program that advances the science of risk assessment, is a key feature of Task 8.2.1. The NexGen Risk Assessment program will perform realistic case studies to evaluate CSS products that incorporate CSS utility evaluation criteria and metrics, while developing best practices for the use of CSS data in science and risk assessments. Task 8.2.2 will address longer-term objectives, including applying value of information analyses. Task 8.2.3 will identify and communicate CSS Program improvement practices. In all, the effort will focus on evaluating the outputs from other CSS Themes to determine if and how they will best be utilized in multiple types of EPA assessments (e.g., human health, exposure, ecological, life-cycle, etc), risk management, and decision-making. As such, the evaluation is focused on discerning the role of CSS products in informing current or future decision-making of the Agency. Evaluation will identify overarching challenges for the CSS program that can be addressed through future enhancements and developments. Thus, an important aspect of evaluation is that the task outputs from this topic will feed back into other CSS topics.

Rationale and Research Approach

Evaluation performed within CSS must determine that the Programs outputs are fit for purpose. This includes both short-term and long-term needs. It is conceivable that an output may be fit for immediate purpose, but that in the long-term the fitness diminishes. Or, it could also be that the long-term needs of the Partner are not well understood initially, causing a disconnect between the products being delivered, and their uses. Thus it is necessary for CSS to provide long-term evaluation of CSS product utility. This can be accomplished through many means, including 1) surveys of our Program Partners, 2) meetings and workshops to look back at varying points to judge product utility, and 3) communications with Partners to identify how their needs have changed. The final product of this effort will be a series of Long-Term Evaluation Reports.

Outputs from Projects related to this task

Evaluation of CSS product utility prior to and following product delivery to the Partners; continuing improvement of the CSS Program through feedback from the evaluation process and from Partners.

Expected Products

(1) Long-term evaluation of CSS product utility through periodic surveys, interviews, and workshops with CSS Partners

Type: OTHER Delivery Date (FY): 2016

Start Date Q1 2012 **End Date** Q4 2016

Cross Research Project Output Supported? Maybe

Could NCER contribute to this task? Maybe

Internal Collaborators (known or proposed)

Potential team members include the following: Hisham El-Masri, Lyle Burgoon, Monica Linnenbrink, Sue Euling, Michael Davis, and selected program and regional offices representatives.

External Collaborators (known or proposed)

TBD

Milestones

(Product 1) Initial Long-term Evaluation Report for FY12 CSS Key Products completed based on Partner feedback	Scheduled: Q1 - 2014 Completed:
(Product 1) Draft Long-term Evaluation Report execution plan developed	Scheduled: Q1 - 2012 Completed:
(Product 1) Long-term Evaluation Report execution plan released, with feedback from Partners incorporated	Scheduled: Q2 - 2012 Completed:

Division Approved Yes